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180. *Photochemical Transformations. Part I. Some Preliminary Investigations.*

By D. H. R. Barton, P. de Mayo, and Mohammed Shafiq.

The main photochemical transformation product of santonin in aqueous acetic acid, "*iso*photosantonic lactone," has been shown to be 10-hydroxy-3-oxoguai-4-en-6 : 12-olide (IV).

Prediction of the structures of photochemical transformation products is difficult, the types of reaction being frequently without analogy in non-photochemical processes. It is certain, however, that photochemical changes may run against the direction of thermodynamic free-energy change in ordinary chemical reactions and that the absorption of light quanta provides a means for the *specific* activation of individual molecules.

Interest by organic chemists in photochemical transformations has been maintained by, for example, the complex sequence of structural changes induced by light in steroidal 5 : 7-dienes [1] as well as by processes of a less exotic kind.[2] We would cite the elegant papers by Büchi and his collaborators [3] as exemplifying the interesting types of photochemical change still awaiting discovery and exploitation.

It is the purpose of our own papers to investigate, first, specific photochemical transformations and, secondly, the mechanisms of such processes, with the ultimate object of prediction. Our personal interest in this field was first stimulated some years ago by the discovery, by Dr. E. L. Wheeler (now of Harvard University) working in our laboratories, that homoannular *cyclo*hexadienones in general were subject to rapid photochemical change. One of the most accessible of these compounds is santonin. In the present paper we elucidate the course of a rearrangement of this compound induced by light.

Prior knowledge of the photochemical transformation products of santonin (I) has been adequately summarised elsewhere [4] and we content ourselves on this occasion with the citation of only references specific [5, 6, 7, 8] to the chemistry of "*iso*photosantonic acid." This compound is, in our hands, the main product, obtainable in 30% yield or more, of irradiation of santonin with ultraviolet light in aqueous acetic acid. These conditions are as approximate to those of the earlier workers (who used sunlight over a period of weeks) as Glasgow weather permits. No yield was indicated in the earlier work.[8] The so-called "photosantonic acid" is formed at the same time in minor amount.

"*iso*Photosantonic acid" was assigned the composition $C_{15}H_{22}O_5$ and was stated to lose water very easily at 100°, or on treatment with acetyl chloride, to furnish "*iso*photosantonic lactone," $C_{15}H_{20}O_4$. In fact both substances are neutral γ-lactones (infrared bands at 1776 cm.$^{-1}$ in Nujol), and the so-called acid is merely the hydrated form of "*iso*photosantonic lactone." Recrystallisation from aqueous solvent affords the hydrated material; from anhydrous solvents the non-hydrated form results. The earlier work showed that the lactone contained one hydroxyl group (formation of an acetate with sodium acetate–acetic anhydride) and one functionally reactive carbonyl group (formation of an oxime, an acetate oxime, and a phenylhydrazone) which was provisionally regarded as aldehydic. In fact, the lactone is stable to chromic acid in acetic acid at room temperature and gives none of the usual aldehyde colour tests. The hydroxyl group must

[1] For example, Havinga, Koevoet, and Verloop, *Rec. Trav. chim.*, 1955, **74**, 1230; Fieser and Fieser, "Natural Products related to Phenanthrene," Reinhold Publ. Corp., New York, 1949, pp. 167 *et seq.*
[2] *Inter al.*, Mustafa, *Chem. Rev.*, 1952, **51**, 1; Schönberg *et al.*, *J. Amer. Chem. Soc.*, 1956, **78**, 1224 and previous papers; Schenk and Dunlap, *Angew. Chem.*, 1956, **68**, 248; Schenk *et al.*, *Annalen*, 1953, **584**, 125, 156, 177, 199, 221; Horner and Spietschka, *Chem. Ber.*, 1955, **88**, 934 and earlier papers.
[3] Büchi, Kofron, Koller, and Rosenthal, *J. Amer. Chem. Soc.*, 1956, **78**, 876, and previous papers.
[4] Simonsen and Barton, "The Terpenes," Cambridge Univ. Press, 1952, Vol. III, p. 292.
[5] Villavecchia, *Atti R. Accad. Lincei*, 1885, **1**, 722; *Ber.*, 1885, **18**, 2859.
[6] Cannizzaro and Fabris, *ibid.*, 1886, **2**, I, 450; *Ber.*, 1886, **19**, 2261.
[7] Francesconi and Villavecchia, *Gazzetta*, 1902, **32**, I, 315.
[8] Francesconi and Venditti, *ibid.*, 1902, **32**, I, 318.

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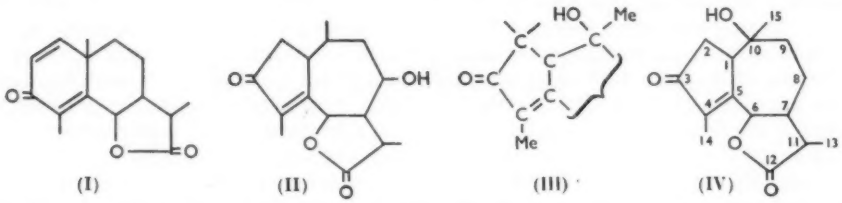
therefore be tertiary and the reactive carbonyl group a ketonic function. The lactone showed infrared bands at 3470 (OH), 1776 (mentioned above), 1693 (CO of *cyclo*pentenone) and 1660 cm.$^{-1}$ (conjugated ethylenic linkage of *cyclo*pentenone). The presence of the *cyclo*pentenone grouping was supported by the ultraviolet absorption which included a strong band at 239 mμ (ε 13,000), corresponding [9] to a fully substituted *cyclo*pentenone as in deacetyl*neo*tenulin (II) which shows [10] $\lambda_{max.}$ 240 mμ (ε 16,000).

Treatment of "*iso*photosantonic lactone" with pyridine–thionyl chloride gave an anhydro-compound containing the system $>C{=}CH_2$, demonstrated by the infrared spectrum [bands at 1770 (γ-lactone), 1690 and 1643 (*cyclo*pentenone), and 906 cm.$^{-1}$ ($>C{=}CH_2$) in $CHCl_3$] and by *C*-Me determinations (three *C*-Me in the parent compound, only two in the anhydro-derivative). The original lactone, therefore, contains the grouping $>CMe{\cdot}OH$. Since the ultraviolet absorption spectrum of the anhydro-derivative is essentially the same as that of the parent lactone the methylene grouping is not conjugated with the same system. In contrast, dehydration of the parent lactone under acidic conditions gave an oily conjugated dienone ($\lambda_{max.}$ 305 mμ) characterised as its 2 : 4-dinitrophenylhydrazone.

Ozonolysis of the lactone followed by steam-distillation gave acetic acid and a neutral compound, $C_{13}H_{16}O_5$, $[\alpha]_D$ −31° (in pyridine). This did not show a hydroxyl band in the infrared spectrum and clearly had two γ-lactone bands (1777 and 1760 cm.$^{-1}$). The presence of a ketone grouping was indicated by oxime formation, by the ultraviolet absorption maximum at 294 mμ (ε 50), and by an infrared band at 1720 cm.$^{-1}$. The formation of acetic acid on ozonolysis of an αβ-unsaturated ketone, as in the case of deacetyl*neo*tenulin,[10] implies the presence of the system $\cdot CO{\cdot}CMe{:}C<$. It is clear, in addition, that the original hydroxyl group must be involved in lactonisation with the carboxyl group generated by fission of the enone system in order to explain the disappearance of the hydroxyl band and the appearance of *two* γ-lactone bands in the compound $C_{13}H_{16}O_5$.



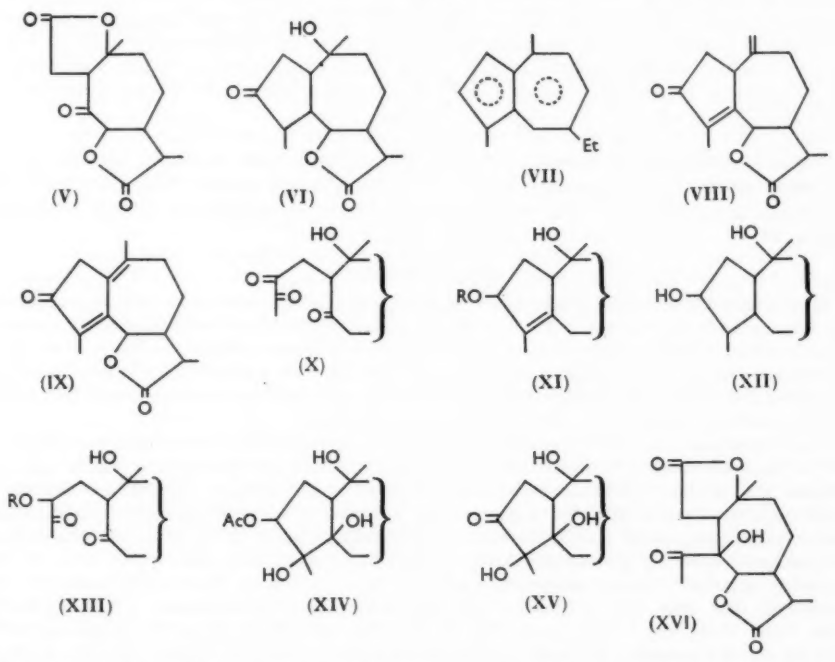
One can therefore write the partial expression (III) for "*iso*photosantonic lactone" and, if one has regard to the constitution of its precursor santonin (I), the interesting structure (IV) for the photo-lactone. The ozonolysis product $C_{13}H_{16}O_5$ can then be formulated satisfactorily as (V). The structure (IV), 10-hydroxy-3-oxoguai-4-en-6 : 12-olide,* was confirmed in a simple manner. Whilst hydrogenation under neutral conditions gave a crystalline dihydro-compound (VI), acid-catalysed hydrogenation afforded a mixture of alcohols (no *cyclo*pentenone band in the infrared region), dehydrogenated over palladised charcoal to chamazulene [12] (VII). The anhydro-compounds mentioned above can then, of course, be formulated as (VIII) for the non-conjugated isomer and (IX) for the conjugated dienone.

* We adopt here the proposal by Šorm and his co-workers [11] that such lactones should be named in terms of guaianolide. The numbering we employ is convenient in that it shows the relation of the guaiane skeleton to the santanic acid or eudesmane skeleton. It also corresponds to steroid and polyterpenoid numbering and may have implications in terms of absolute configuration.

[9] Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 76; Gillam and West, *J.*, 1942, 486.
[10] Barton and de Mayo, *J.*, 1956, 142.
[11] Cekan, Herout, and Šorm, *Chem. and Ind.*, 1954, 604.
[12] Meisels and Weizmann, *J. Amer. Chem. Soc.*, 1953, **75**, 3865; Šorm, Herout, and Takeda, *Chem. Listy*, 1954, **48**, 281; Novak, Šorm, and Sicher, *ibid.*, p. 1648.

The novel constitution (IV) for the photo-product was supported by the following experiments. A more detailed study of its ozonolysis showed that, if the ozonide was decomposed hydrolytically but without steam-distillation, an isomeric neutral $C_{13}H_{16}O_5$ compound, $[\alpha]_D$ +70° (in pyridine), resulted. The infrared spectrum of this (in Nujol) showed no hydroxyl band, two γ-lactone bands (at 1777 and 1750 cm.$^{-1}$) and a ketone band (at 1720 cm.$^{-1}$). The pyridine solution mutarotated to −31° in 18 hr. and the first-mentioned $C_{13}H_{16}O_5$ compound was formed in quantitative yield. It is obvious that the two compounds are stereoisomers at one or both of the asymmetric centres α to the ketone group and that steam-distillation is a sufficiently vigorous process to provoke the isomerisation. When the ozonide was decomposed by hydrogenation, the triketone (X), $C_{15}H_{20}O_6$, resulted. This is not unexpected on mechanistic grounds.[13] Treatment of this triketone (X) with alkaline hydrogen peroxide afforded, in accordance with the α-diketone formulation, one mol. of acetic acid.

Reduction of the photo-product (IV) with sodium borohydride gave the unsaturated alcohol (XI; R = H) and the corresponding saturated alcohol (XII). Ozonolysis of the former alcohol afforded the corresponding diketo-alcohol (XIII; R = H), and acetylation gave an oily monoacetate (XI; R = Ac) characterised by ozonolysis to the crystalline acetoxy-diketone (XIII; R = Ac). Treatment of the unsaturated acetate (XI; R = Ac) with osmium tetroxide gave a crystalline α-glycol (XIV) which consumed periodic acid only slowly. In a corresponding experiment, the photo-product (IV) itself was treated with osmium tetroxide and thus converted into a glycol (XV). In contrast to the previous

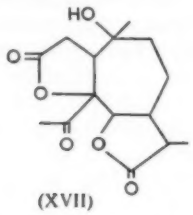


glycol (XIV), this trihydroxy-ketone (XV) consumed one mol. of periodic acid or lead tetra-acetate very rapidly, to give a neutral dilactone $C_{15}H_{20}O_6$. This substance was shown to be identical with the so-called "bishydroxy*iso*photosantonic acid" obtained earlier [8] by oxidation of the photo-product (IV) with potassium permanganate. In the

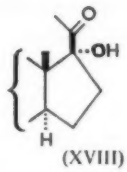
[13] Barton and Seoane, *J.*, 1956, 4150.

infrared spectrum the oxidation product showed bands at 3430 (OH), 1760 (strength indicative of two γ-lactones), and 1710 cm.$^{-1}$ (aliphatic CO or equivalent), the last assignment being confirmed by the ultraviolet absorption spectrum ($\lambda_{max.}$ at 295 mμ; ε 40). The compound was stable to chromic acid, showing that the hydroxyl group was tertiary, and gave a positive iodoform test. It can, therefore, be formulated as (XVI) or (XVII). In so far as there is analogy in (V) for the lactone system of (XVI), and in so far as the oxidation product could not be dehydrated with thionyl chloride and pyridine under conditions which dehydrate (IV) readily, we favour structure (XVI). The resistance of this compound to further oxidation by periodic acid or lead tetra-acetate is, perhaps, evidence in favour of structure (XVII), except that steroidal 17α-hydroxy-20-ketones of the partial structure (XVIII) are notoriously resistant [14] to these reagents.

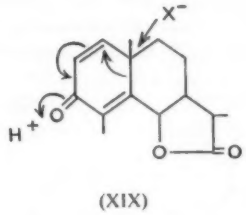
The mechanism of the rearrangement of santonin to 10-hydroxy-3-oxoguai-4-en-6 : 12-olide (IV) can possibly be visualised as follows. Photoactivation of santonin provides sufficiently energised molecules for occurrence of the acid-catalysed rearrangement shown in (XIX) or equivalent. The anion X^- which is added at $C_{(10)}$ can either be hydroxyl from water, as in the present case and in that of the investigations by Francesconi and Venditti,[8] or acetate, from the glacial acetic acid employed in some experiments by the Italian workers.



(XVII)



(XVIII)



(XIX)

We are studying other aspects of the photochemistry of santonin, as well as the generality of the rearrangement reported in the present paper. We are particularly concerned to effect such rearrangements with the physiologically active 1-dehydrosteroids.[15]

Experimental

M. p.s were taken on the Köfler block unless specified to the contrary. Ultraviolet absorption spectra were determined in EtOH solution with the Unicam S.P. 500 Spectrophotometer. Infrared spectra were kindly determined by Dr. G. Eglinton and his colleagues for Nujol suspensions except as otherwise qualified. $[\alpha]_D$ are in $CHCl_3$ unless stated otherwise. Light petroleum refers to the fraction of b. p. 40—60°. Microanalyses were carried out by Mr. J. M. L. Cameron, Miss M. W. Christie, and their associates.

iso*Photosantonic Lactone* (10-*Hydroxy*-3-*oxoguai*-4-*en*-6 : 12-*olide* (IV).—Santonin (4·0 g.) in 4 : 5 acetic acid–water (110 ml.) was irradiated in a quartz flask under reflux with a bare mercury-arc (125 w) lamp until the rotation fell to approx. 2° (~7 hr.). Removal of the solvent under reduced pressure afforded a gum which was separated by means of sodium hydrogen carbonate into acidic and neutral fractions. The neutral fraction (3·2 g.) was chromatographed over silica gel (110 g.), 20 fractions being collected. Elution with ether–acetone (1 : 2) (four fractions) afforded "*iso*photosantonic lactone" (1·2 g.), m. p. (from ethyl acetate–light petroleum) 165—167°, $[\alpha]_D$ +129° (*c* 1·34), $\lambda_{max.}$ 239 mμ (ε 13,000) (Found : C, 68·2; H, 7·35; *C*-Me, 17·5. Calc. for $C_{15}H_{20}O_4$: C, 68·15; H, 7·65; 3*C*-Me, 17·0%). Crystallisation from aqueous ethanol afforded material of the same m. p. (Found : C, 64·05; H, 7·6. Calc. for $C_{15}H_{20}O_4,H_2O$: C, 63·8; H, 7·85%). The compound gave negative Schiff, Angeli–Rimini, and Fehling tests.

The acidic fraction (760 mg.) was chromatographed over silica gel (27 g.) (20 fractions).

[14] For example, Brooks and Norymberski, *Biochem. J.*, 1953, **55**, 371.
[15] Herzog, Payne, Jevnik, Gould, Shapiro, Oliveto, and Hershberg, *J. Amer. Chem. Soc.*, 1955, **77**, 4781; Nobile, Charney, Perlman, Herzog, Payne, Tully, Jevnik, and Hershberg, *ibid.*, p. 4184.

Elution with benzene–ether (5 : 1) (4 fractions) gave photosantonic acid (160 mg.), m. p. (from chloroform–light petroleum) 154—155°, $\lambda_{max.}$ 210 mμ (ε 6700), $[\alpha]_D$ −129° (*c* 1·3) (Found: C, 68·4; H, 7·6. Calc. for $C_{15}H_{20}O_4$: C, 68·15; H, 7·65%). Further elution with ether–acetone (2 : 1) (3 fractions) afforded some "*iso*photosantonic lactone" (144 mg.).

Photosantonic acid, on crystallisation from aqueous ethanol, formed a hydrate, sintering below 100° and melting at 154—155° (Found: C, 64·2; H, 7·1. Calc. for $C_{15}H_{20}O_4,H_2O$: C, 63·8; H, 7·85%). Both the hydrated and the anhydrous form of photosantonic acid showed γ-lactone bands in the infrared spectrum, and the relation between the forms is the same as that between the hydrated and the anhydrous form of "*iso*photosantonic lactone" (see above). We hope to discuss this matter in more detail in a further communication.

The acetate of "*iso*photosantonic acid lactone" was prepared by Cannizzaro and Fabris's [6] method. Recrystallised from ethyl acetate–light petroleum it had m. p. 175—177° (capillary), $[\alpha]_D$ +58° (*c* 0·53 in EtOH), $\lambda_{max.}$ 239 mμ (ε 13,000). Cannizzaro and Fabris recorded m. p. 183°, $[\alpha]_D$ +59° (in EtOH). The acetate showed infrared bands at 1770 (γ-lactone), 1730 and 1260 (acetate), 1703 and 1635 cm.$^{-1}$ (*cyclo*pentenone).

3-Oxoguai-4 : 10(15)-dien-6 : 12-olide (VIII).—10-Hydroxy-3-oxoguai-4-en-6 : 12-olide (IV) (56 mg.) in pyridine (3 ml.) was treated with thionyl chloride (240 mg.) at 0° for 10 min. Isolation of the product and chromatography over silica gel (2 g.) (six fractions) gave, on elution with benzene (two fractions), *3-oxoguai-4 : 10(15)-dien-6 : 12-olide* (VIII) (20 mg.), m. p. (from ethyl acetate–ether–light petroleum) 113—115°, $\lambda_{max.}$ 236 mμ (ε 12,600), $[\alpha]_D$ +378° (*c* 1·21) (Found: C, 73·15; H, 7·1; *C*-Me, 14·9. $C_{15}H_{18}O_3$ requires C, 73·15; H, 7·35; 2*C*-Me, 12·2%). Ozonolysis of the anhydro-compound (73 mg.) in methylene dichloride (50 ml.) at −30° for 30 min. (disappearance of ultraviolet max. at 236 mμ), followed by steam-distillation into aqueous dimedone after removal of methylene dichloride *in vacuo*, gave the formaldehyde–dimedone compound (17·8 mg., 20%), identified by m. p. and mixed m. p. Similar ozonolysis of the anhydro-compound (65 mg.), followed by conversion of the acidic portion of the steam-distillate into the *p*-bromophenacyl ester, gave, after chromatography over alumina (2 g.; Brockmann grade 5), *p*-bromophenacyl acetate (29 mg., 50%), identified by m. p. and mixed m. p.

Acid-catalysed Dehydration of 10-Hydroxy-3-oxoguai-4-en-6 : 12-olide (IV).—The hydroxy-lactone (300 mg.) in acetic acid (10 ml.) was treated on the steam-bath for 45 min. with a 7% solution (30 ml.) of perchloric acid in acetic acid. Chromatography of the product over silica (9 g.) gave, on elution with benzene and with benzene–ether (2 : 1), a gum showing $\lambda_{max.}$ 305 mμ (ε 11·300). This was converted into the 2 : 4-dinitrophenylhydrazone in the usual way. Chromatography over bentonite–Celite and elution with chloroform gave *3-oxoguai-4 : 1(10)-dien-6 : 12-olide* (IX) *2 : 4-dinitrophenylhydrazone*, m. p. (from chloroform–ethanol) 232—238° (decomp.), $\lambda_{max.}$ 405 mμ (ε 26,600 in $CHCl_3$) (Found: N, 13·4. $C_{21}H_{22}O_6N_4$ requires N, 13·15%), infrared band at 1765 cm.$^{-1}$ (γ-lactone).

Ozonolysis of 10-Hydroxy-3-oxoguai-4-en-6 : 12-olide (IV).—(*a*) The keto-lactone (100 mg.) in chloroform (40 ml.) was ozonised at −10° for 25 min. (disappearance of band at 239 mμ). Steam-distillation and conversion of the volatile acidic portion into the *p*-bromophenacyl ester (removal of $CHCl_3$ *in vacuo*) gave, on chromatography over alumina (2·5 g.; Brockmann grade 5) and elution with benzene–light petroleum (b. p. 60—80°) (1 : 20), *p*-bromophenacyl acetate (20 mg., 20%), identified by m. p. and mixed m. p. The residue from the steam-distillation afforded the stable *2 : 5-dihydroxy-5-methyl-3-oxocycloheptane-4-acetic-1-α-propionic dilactone* (V), m. p. (from ethyl acetate) 198—212° (decomp.), $[\alpha]_D$ −31° (*c* 0·80 in pyridine), $\lambda_{max.}$ 294 mμ (ε, 50) (Found: C, 61·8; H, 6·65; *C*-Me, 12·25%; equiv., 126·1, 126·4. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4; 2*C*-Me, 11·9%; equiv., 126·1). This compound gave a positive Fehling's test, but was stable to chromic acid in acetic acid at room temperature during 1½ hr. Its *oxime*, prepared with pyridine–hydroxylamine hydrochloride in the usual way, had m. p. (from methanol–ether–light petroleum) 214—224° (decomp.), $[\alpha]_D$ +90° (*c* 0·66) (Found: C, 58·25; H, 6·1; N, 5·75. $C_{13}H_{17}O_5N$ requires C, 58·4; H, 6·4; N, 5·25%).

(*b*) A similar ozonolysis, but with decomposition of the ozonide with cold water, furnished the labile *dilactone* (V), m. p. (from ethyl acetate) 198—212° (decomp.), $[\alpha]_D$ +70° (*c* 0·69 in pyridine) (Found: C, 61·7; H, 6·65%). After 18 hr. in pyridine the rotation had changed to −31°, characteristic of the stable dilactone (see above). Isolation gave the stable dilactone itself, identified by m. p., rotation, and infrared spectrum.

(*c*) 10-Hydroxy-3-oxoguai-4-en-6 : 12-olide (70 mg.) in ethyl acetate (5 ml.) was ozonised

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at −60° for about 30 min. (disappearance of ultraviolet max. at 239 mμ). Palladised charcoal was added and the solution hydrogenated as it warmed to room temperature. Crystallisation from ethanol–light petroleum gave the *triketone* {α-[4-(2 : 3-*dioxobutyl*)-2 : 5-*dihydroxy*-5-*methyl*--3-*oxo*cyclo*heptyl*]*propionic* 2-*lactone*} (X), m. p. 154—156°, $[\alpha]_D$ +20° (*c*, 0·66 in ethanol), $\lambda_{max.}$ 290 mμ (ε, 71) (Found : C, 61·05; H, 6·5. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8%). The compound gave a positive Fehling's test but was not cleaved by lead tetra-acetate in acetic acid at room temperature. Treatment of the triketone (54 mg.) in ethanol (5 ml.) containing aqueous 4N-sodium hydroxide (1 ml.) with 30% hydrogen peroxide (3 ml.) for 15 min. (excess of peroxide destroyed with platinum black) gave, on acidification with diluted sulphuric acid and steam-distillation, acetic acid (0·9 mol. by titration), characterised as the *p*-bromophenacyl ester (m. p. and mixed m. p.), as sole volatile product.

10-*Hydroxy*-3-*oxoguaian*-6 : 12-*olide*.—10-Hydroxy-3-oxoguai-4-en-6 : 12-olide (1·0 g.) in ethanol (100 ml.) was hydrogenated over 5% palladised charcoal (500 mg.) for 3 hr. (uptake of 1 mol. of hydrogen). Chromatography of the product over silica gel (35 g.) (17 fractions) afforded, on elution with ether (6 fractions), 10-*hydroxy*-3-*oxoguaian*-6 : 12-*olide* (VI), m. p. (from ethyl acetate–benzene–light petroleum) 135—138°, $[\alpha]_D$ −46° (*c* 1·16) (Found : C, 67·45; H, 8·1. $C_{15}H_{22}O_4$ requires C, 67·65; H, 8·35%).

Oxidation of 10-*Hydroxy*-3-*oxoguai*-4-*en*-6 : 12-*olide with Potassium Permanganate*.—The hydroxy-lactone was oxidised with potassium permanganate as described by Francesconi and Venditti [8] to furnish the dilactone (XVI). Recrystallised from ethyl acetate this had m. p. 286—288°, $[\alpha]_D$ +34° (*c* 1·0), $[\alpha]_D$ +112° (*c* 0·67 in pyridine), $\lambda_{max.}$ 295 mμ (ε 40) (Found : *C*-Me, 16·1. $C_{15}H_{20}O_6$ requires 3*C*-Me, 15·2%). The compound gave a positive iodoform test and was stable to chromic acid for 2 hr. at 60° in acetic acid. It was not dehydrated by thionyl chloride–pyridine at 0° or at room temperature (recovered unchanged).

This dilactone was also obtained in the following way. 10-Hydroxy-3-oxoguai-4-en-6 : 12-olide (50 mg.) in dry dioxan (0·5 ml.) was treated with osmium tetroxide (63 mg.) for 4 days at room temperature. Cleavage of the osmate with hydrogen sulphide and crystallisation of the product from methanol–ethyl acetate–light petroleum afforded 4 : 5 : 10-*trihydroxy*-3-*oxoguaian*-6 : 12-*olide* (XV), m. p. 193—198° (decomp.), $[\alpha]_D$ −17° (*c* 1·02), infrared bands at 3400 (OH), 1760 (γ-lactone) and 1740 cm.$^{-1}$ (*cyclo*pentanone) (Found : C, 59·95; H, 7·65. $C_{15}H_{22}O_6$ requires C, 60·4; H, 7·45%). This triol consumed 0·96 mol. of periodic acid in 15 min. after which there was no further uptake of oxidant. Consumption of lead tetra-acetate in acetic acid was the same. The triol (90 mg.) in water (45 ml.) was treated with 0·05N-periodic acid (27 ml.) until one mol. of oxidant had been consumed (15 min.). Crystallisation of the product from ethyl acetate gave the dilactone (XVI) (see above), identified by m. p., mixed m. p., rotation {$[\alpha]_D$ +113° (*c* 0·62 in pyridine)}, and infrared spectrum (Found : C, 60·55; H, 6·85. Calc. for $C_{15}H_{20}O_6$: C, 60·8; H, 6·8%).

Reduction of 10-*Hydroxy*-3-*oxoguai*-4-*en*-6 : 12-*olide with Sodium Borohydride*.—The hydroxy-lactone (300 mg.) in ethanol (2 ml.) was treated with sodium borohydride (400 mg.) in the same solvent (3 ml.) for 90 min. Crystallisation of the product from ethyl acetate–light petroleum furnished 3 : 10-*dihydroxyguai*-4-*en*-6 : 12-*olide* (XI; R = H), m. p. 205—208°, $[\alpha]_D$ +87° (*c* 0·86), no high-intensity ultraviolet absorption (Found : C, 67·6; H, 8·45. $C_{15}H_{22}O_4$ requires C, 67·65; H, 8·35%). Acetylation (pyridine–acetic anhydride at room temperature overnight) gave an oily monoacetate to which further reference is made below.

Fractional crystallisation of the mother-liquors from the sodium borohydride reduction from methanol–ethyl acetate–light petroleum gave the saturated 3 : 10-*dihydroxyguaian*-6 : 12-*olide* (XII), m. p. 95—97°, $[\alpha]_D$ +16° (*c* 0·82) (Found : C, 63·0; H, 9·0. $C_{15}H_{24}O_4,H_2O$ requires C, 62·9; H, 9·15%).

Ozonolysis of 3 : 10-dihydroxyguai-4-en-6 : 12-olide (100 mg.) in chloroform (100 ml.) at −25° for 30 min., decomposition of the ozonide with water, and crystallisation of the product from ethyl acetate–light petroleum afforded the *dihydroxy-diketone* {α-[2 : 5-*dihydroxy*-4-(2-*hydroxy*-3-*oxobutyl*)-5-*methyl*-3-*oxo*cyclo*heptyl*]*propionic* 2-*lactone*} (XIII; R = H), m. p. 196—208° (decomp.), $[\alpha]_D$ −8° (*c* 0·58 in pyridine) (Found : C, 60·75; H, 7·45. $C_{15}H_{22}O_6$ requires C, 60·4; H, 7·45%). Similar ozonolysis of the oily acetate gave the *acetate* (XIII; R = Ac), m. p. (from ethyl acetate–light petroleum) 178—181°, $[\alpha]_D$ +104° (*c* 1·04) (Found : C, 57·15; H, 7·45. $C_{17}H_{24}O_{7},H_2O$ requires C, 56·95; H, 7·3%). The compound gave a positive Fehling's test.

Treatment of the oily acetate (47 mg.) in dioxan (6 ml.) with osmium tetroxide (56 mg.) for

14 days at room temperature and cleavage of the derived osmate with hydrogen sulphide gave 3-*acetoxy*-4 : 5 : 10-*trihydroxyguaian*-6 : 12-*olide* (XIV), m. p. (from methanol–ethyl acetate–light petroleum) 192—194°, $[\alpha]_D$ +19° (*c* 0·95) (Found: C, 58·25; H, 7·45. $C_{17}H_{26}O_7,\frac{1}{2}H_2O$ requires C, 58·15; H, 7·75%). This compound consumed 1·1 mol. of periodic acid during 18 hr. at room temperature after which there was no further uptake.

Dehydrogenation.—10-Hydroxy-3-oxoguai-4-en-6 : 12-olide (1·0 g.) in "AnalaR" acetic acid (80 ml.) containing 72% perchloric acid (5 drops) was hydrogenated at a platinum catalyst. The gummy product (no ketonic band group in the infrared spectrum) was dehydrogenated in portions (200 mg.) by heating it with 10% palladised charcoal (200 mg.) for 15 min. under nitrogen at 320° (Wood's-metal bath). The combined product was extracted with light petroleum (b. p. 60—80°), and the blue solution filtered through alumina (5 g.; Brockmann grade 5), the column being further developed with benzene–light petroleum (b. p. 60—80°) (1 : 2). The combined eluates were extracted with 80% phosphoric acid to concentrate the azulenic material. Isolation from the phosphoric acid solution in the usual way gave, on treatment with trinitrobenzene, the chamazulene–trinitrobenzene adduct (equiv. to 6·2 mg. of chamazulene), identified by m. p., mixed m. p. and ultraviolet and visible absorption spectra.

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THE UNIVERSITY, GLASGOW, W.2. [*Received, September 13th,* 1956.]

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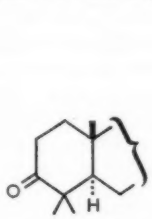
181. *Long-range Effects in Alicyclic Systems. Part II.* The Rates of Condensation of Some Triterpenoid Ketones with Benzaldehyde.*

By D. H. R. BARTON, A. J. HEAD, and P. J. MAY.

The rates of base-catalysed condensation of a series of triterpenoid 3-ketones with benzaldehyde have been determined. When lanost-8-enone is taken as a standard and ring A and part of ring B are kept constant, variations in rate over a factor of 43 can be demonstrated. It has been shown that neither electrostatic nor bond-induction effects will explain the rate anomalies observed. A new effect has, therefore, been postulated and described as "conformational transmission." An account of some of the results and a definition of the new effect were published [1] in preliminary form.

IT is the purpose of this series of investigations to explore the nature of the interaction of functional groups within saturated alicyclic systems. The present paper is concerned with the rate of condensation of benzaldehyde with triterpenoid 3-ketones, all of which have partial structure (I), to give benzylidene derivatives (II). This reaction was selected



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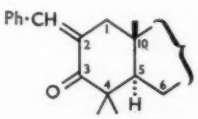

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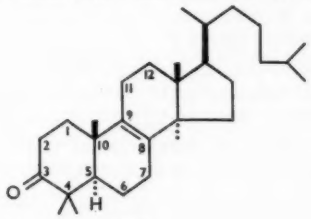

(III)

for the following reasons. (i) The rate of condensation catalysed by 0·1N-base at 25·0° for the standard ketone lanost-8-enone (III) proceeds at a convenient speed which can be determined by following the appearance of the band at 292 mμ characteristic of the system

* Part I, *J.*, 1956, 932.

[1] Barton, *Experientia*, 1955, Suppl. II, 121 (summary of a Section lecture, Internat. Congr. Pure Appl. Chem., Zürich, July, 1955).

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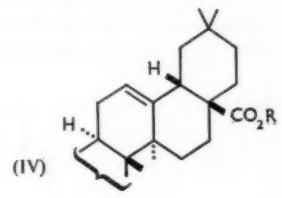
(II). (ii) A large variety of different ketones of defined constitution, configuration, and rigid conformation can be obtained easily. (iii) The kinetics of such condensations have been investigated [2,3,4,5] and it is established that the rate is of the first order with respect to aldehyde and ketone and almost certainly [2,3] also with respect to base. Since the actual kinetic orders for the reactants are not important for our present purpose, all reactions were run in 99% v/v aqueous ethanol at the same concentration (0·1N) of potassium hydroxide at 25·0°. A known excess of benzaldehyde (about 10 : 1 molar) was employed so that the actual reaction kinetics (with respect to the appearance of the 292 mμ band) were of the first order. Preliminary experiments indicated also the expected first-order relation in benzaldehyde. Since, however, all discussion is concerned with rates relative to lanost-8-enone (III), our purpose only required that all variables, except the structure of the ketone, be kept constant. In order to ensure complete reliability the rate of reaction of the ketone (III) was always determined at the same time as the rate of reaction of the ketone under investigation: results (see Table) are summarised as percentages of the lanost-8-enone rate. This does not imply that there were large variations in the latter; it does, however, illustrate the precautions that we have tried to take in order to ensure that the differences in rate are indeed significant. The error in our measurements is not easy to determine but we are convinced that it is at least less than ±5% (relative, not absolute). All ketones examined were, of course, specially purified.

Compound	No. of runs	Average rate : % of lanost-8-enone rate	Limiting values
Masticadienonic acid (V; R = H)	2	8	6·3—9·8
Methyl masticadienonate (V; R = Me)	2	8	8·1—8·4
Lanost-7-enone (VI)	2	17	16·4—16·9
Lanosta-7 : 9(11)-dienone (VII)	3	44	43·1—45·3
Lanostanone (VIII)	2	55	54·7—56·1
α-Amyrene-3 : 11-dione (XV)	2	75	72·8—77·5
β-Amyrene-3 : 11-dione (XVI)	3	75	71·4—76·6
β-Amyra-12 : 18-diene-3 : 11-dione (XVII)	3	75	70·1—77·5
Oleanone (IX)	2	88	85·8—90·0
Noroleana-16 : 18-dienone (X)	4	91	85·2—96·1
Lupenone (XXIV; R = $CMe{:}CH_2$)	2	95	94·3—95·0
Oleanonic acid (IV; R = H)	2	97	95·9—98·5
Lupanone (XXIV; R = Pr^i)	2	98	97·6—98·1
Lanost-8-enone (III)	—	100	—
α-Amyrone (XXV)	3	100	98·2—103·3
*allo*Betulone (XXVII)	2	100	99·3—100·7
β-Amyrone (XXVI)	4	108	103·3—111
Methyl moronate (XXVIII)	2	108	107—109
Methyl 3 : 19-dioxo-olean-13(18)-enoate (XVIII)	2	111	107—114
Methyl oleanonate (IV; R = Me)	3	113	112—114
α-Amyra-9(11) : 12-dienone (XI)	2	115	115—115
Noroleana-12 : 17-dienone (XII)	2	116	115—118
α-Onoceradienedione (XIII)	2	117	117—118
Dehydro-β-amyrone (XIV; R = Me)	3	124	117—132
Methyl *iso*dehydro-oleanonate (XXIII)	5	128	125—132
Methyl dehydro-oleanonate (XIV; R = CO_2Me)	2	129	129—130
β-Amyrane-3 : 12-dione (XIX)	2	170	166—174
α-Amyr-9(11)-ene-3 : 12-dione (XX)	3	266	263—269
β-Amyr-9(11)-ene-3 : 12-dione (XXI)	2	288	282—294
β-Amyra-9(11) : 13(18)-diene-3 : 12 : 19-trione (XXII)	2	344	344—344

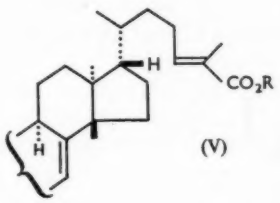
Since partial structure (I) is a common feature for all the ketones under consideration, steric hindrance at $C_{(2)}$ must in a classical sense be constant throughout. This is especially true because of the rigid extended conformations of these compounds. We reject, therefore, the idea that any straightforward steric effect could explain our results. The variations in rate, which range (see Table) over a factor of forty-three, could be of polar

[2] Coombs and Evans, *J.*, 1940, 1295.
[3] Gettler and Hammett, *J. Amer. Chem. Soc.*, 1943, **65**, 1824.
[4] Noyce and Pryor, *ibid.*, 1955, **77**, 1397.
[5] Noyce, Pryor, and Bottini, *ibid.*, p. 1402.

origin. In the saturated type of compound here studied this means that the variation would be produced by an electrostatic effect through space or by bond induction,[6] the two effects being classified together as the inductive effect. We can reject both of these possibilities on the following grounds.



(IV)



(V)

If electrostatic effects were involved, they would be greatest for unit polar charges; indeed the latter should completely dominate any dipolar interactions. In fact the rate for the anion of oleanonic acid (IV; R = H) is not very different from that for methyl oleanonate (IV; R = Me), whilst the rates for the anion of masticadienonic acid* (V; R = H) and the corresponding methyl ester (V; R = Me) are identical.

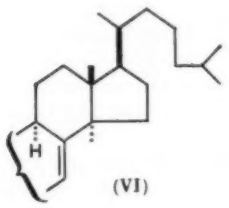
If electrostatic effects due to dipoles were of importance, the compounds containing ketone groups (other than at $C_{(3)}$) should produce much larger deviations from the lanost-8-enone rate than compounds having only ethylenic linkages. This is certainly not correct. Thus lanost-7-enone (VI), lanosta-7 : 9(11)-dienone (VII), and lanostanone (VIII) all react much more slowly, oleanone (IX) and noroleana-16 : 18-dienone (X) react significantly more slowly, whilst α-amyra-9(11) : 12-dienone (XI), noroleana-12 : 17-dienone (XII), α-onocera-dienedione (XIII), and dehydro-β-amyrone (XIV; R = Me) react significantly faster than the standard lanost-8-enone. These are compounds where there are no polar linkages, except in ring A, and where the effects must be due to some special property of ethylenic linkages (see below). The compounds α- (XV) and β-amyrene-3 : 11-dione (XVI), and β-amyra-12 : 18-diene-3 : 11-dione (XVII), have rates which are slower than normal, whilst methyl 3 : 19-dioxo-olean-13(18)-enoate (XVIII) reacts faster. All 12-ketones, β-amyrane-3 : 12-dione (XIX), α- (XX) and β-amyr-9(11)-ene-3 : 12-diones (XXI), and β-amyra-9(11) : 13(18)-diene-3 : 12 : 19-trione (XXII), react considerably faster. There is, however, no obviously greater capacity shown by the compounds with polar linkages over those without in producing rate anomalies. An instructive comparison is provided by dehydro-β-amyrone (XIV; R = Me) and methyl dehydro-oleanonate (XIV; R = CO_2Me), the extra dipole in the latter having no effect on the abnormal rate constant. If it is granted that the methoxycarbonyl group of (XIV; R = CO_2Me) has nothing to do with the enhanced rate, then this must be due to the diene system as it is in (XIV; R = Me). The diene system of *iso*dehydro-oleanonate (XXIII) also, therefore, produces an abnormal rate effect. This conclusion is, however, only justified when one recognises that lupenone (XXIV; R = CMe:CH_2), lupanone (XXIV; R = Pr^i), α- (XXV) and β-amyrone (XXVI), *allo*betulone (XXVII), and methyl moronate (XXVIII) have substantially normal rate constants. From these structures one can see that, in the absence of some disturbing unsaturation, such as a diene system, the partial system (XXIX) confers the same rate constant on a compound as does the system of lanost-8-enone (III).

* The stereochemistry of masticadienonic acid at $C_{(9)}$ was not defined in our earlier papers,[7,8] but its relation to the corresponding centre of butyrospermol was implied. Now that the latter has been convincingly shown[9] to be α-oriented at $C_{(9)}$, the corresponding configurational symbol can be introduced into the formula for masticadienonic acid.

[6] Roberts and Moreland, *J. Amer. Chem. Soc.*, 1953, **75**, 2167.
[7] Barton and Seoane, *J.*, 1956, 4150.
[8] Seoane, *ibid.*, p. 4158.
[9] Lawrie, Hamilton, Spring, and Watson, *J. Org. Chem.*, 1956, **21**, 491.

XUM

There remains for consideration that part of the inductive effect which we can classify as bond induction. In compounds (XV) and (XVI) the rate is depressed. Therefore, if bond induction were important, one would conclude that the transmission of the slight positive charge on the 11-carbon atom had a retarding effect on the rate. Yet compounds (XXI)and (XXII), where the positive charge (at the β-position) is greater *and* closer to $C_{(2)}$ has exactly the opposite effect on the rate. Also compound (XIX) has the same enhanced rate as compounds (XXI) and (XXII) and yet has its positively charged carbon atom two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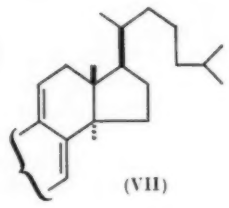
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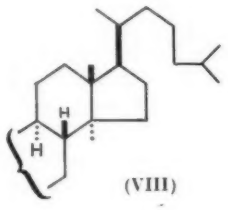
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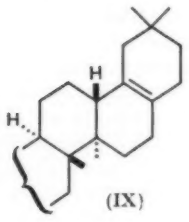
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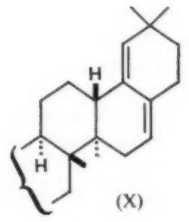
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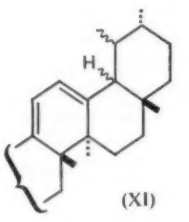
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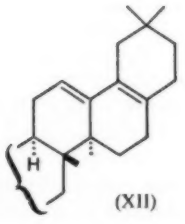
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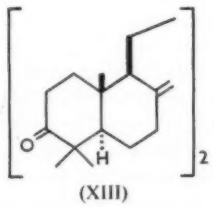
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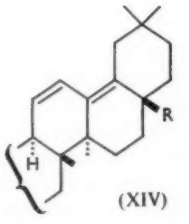
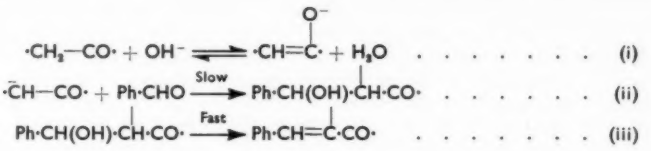

(XIV)

carbon atoms more remote from $C_{(2)}$. Transmission through two extra saturated carbon atoms should of course, greatly reduce any bond-transmission effect. Compound (XVIII), where the fractional positive charge is only one carbon atom more remote, has a rate which is only slightly greater than the standard and not comparable with that for (XIX). On this evidence bond induction can be dismissed as an explanation for our anomalies.

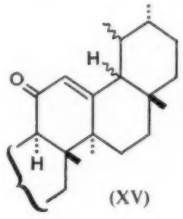
One may also consider if hyperconjugative effects could be operative, although this is not usually recognised as being of significance in saturated systems. By definition such effects must show alternation. Compounds (XI), (XIV; R = Me or CO_2Me), and (XXIII) all show enhanced rates with no indication of alternation. We reject then an explanation based on hyperconjugation.

We are, therefore, forced to admit a new effect which we have defined as follows.[1] The differences in rate from the standard probably arise, in main part, from conformational distortion produced by unsaturated substituents. We imagine that this distortion is transmitted through the saturated molecule by a slight flexing of valency angles and alteration of atomic co-ordinates. The distortion ultimately influences ring A and thus makes a difference from the standard reaction rate (see further below). The new effect may, therefore, be described as "*conformational transmission.*"

The mechanism of the benzaldehyde condensation, defined by its kinetic form, must surely be as follows : [10]



The rate therefore involves the equilibrium (i) and the slow step (ii). Now, as already emphasised (see above), classical steric hindrance for step (ii) is the same for all compounds. We are inclined therefore to the view that the rate constant for step (ii) is also substantially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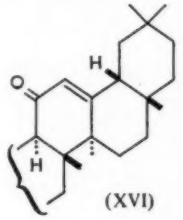
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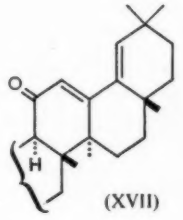
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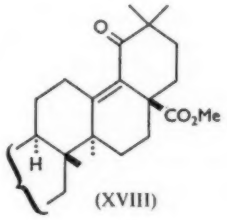

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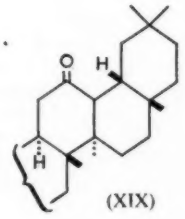
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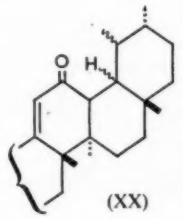
(XX)

the same for all our compounds. If this is correct, conformational transmission must influence the position of the equilibrium (i). That is, for the fast rates the equilibrium is further on the right-hand side than for the slow rates.

The principal factor influencing this equilibrium (i) might well be the 1 : 3-interaction between the axial methyl groups at $C_{(4)}$ and $C_{(10)}$. Thus the markedly slower rate for lanostanone (VIII) than for compounds such as (XXIV; R = CMe:CH_2 or Pr^i) or (XXVI) must be ascribed to the absence of an axial 8-methyl group. The three axial methyl groups at $C_{(4)}$, $C_{(10)}$, and $C_{(8)}$ must interact with each other in the 1 : 3-manner in the other compounds cited.

We feel that further theoretical discussion at this point is premature. A new and subtle conformational effect has however in our view been clearly demonstrated. We are now engaged in measurements on compounds which will define the nature of the effect more closely. In the meantime it will be of interest to see if such subtle conformational factors can be detected by other methods, for example by study of optical dispersion.[11]

The benzylidene compounds formed by condensation at $C_{(2)}$ are somewhat light sensitive. Adequate precautions were taken, therefore, to exclude light. Irradiation with ultraviolet light isomerised the initial benzylidene compounds of $\lambda_{max.}$ 292 mμ to a

[10] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons, Ltd., London, 1953, p. 683.
[11] See Djerassi and Closson, *J. Amer. Chem. Soc.*, 1956, **78**, 3761 and later papers.

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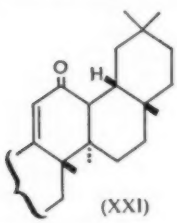
different series of compounds with $\lambda_{max.}$ 276 mμ. Details are given in the Experimental section; the phenomenon is, of course, well known.[12]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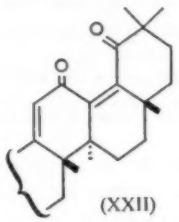
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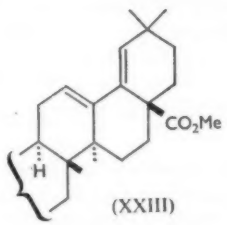
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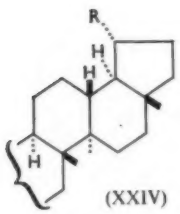
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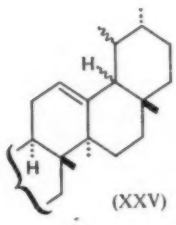
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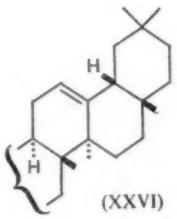
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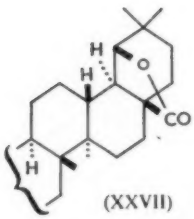
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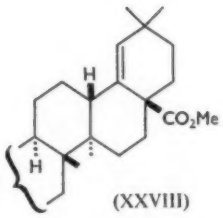
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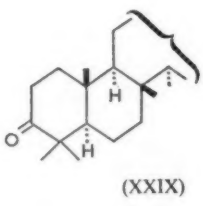
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Experimental

For general experimental details see earlier work.[13] Rotations were taken in $CHCl_3$ solution. Ultraviolet absorption spectra were determined with a Unicam S.P. 500 spectrophotometer. Absolute ethanol was used except for the kinetic runs (see below). Light petroleum refers to the fraction of b. p. 40—60°. Rate measurements were made at 25·0° in a thermostat (±0·03°), flasks being tightly covered with tin-foil. All ketones were thoroughly dried *in vacuo* before being weighed for rate measurements.

Alcohols were oxidised to ketones by the following method.[14] A 10% (w/v) suspension of " AnalaR " chromium trioxide in " AnalaR " pyridine was prepared by cautious addition of the trioxide to the pyridine with cooling. To this was added a 10% (w/v) solution of the alcohol in " AnalaR " pyridine. About six times the theoretical amount of chromium trioxide was employed. For working up, the mixture was diluted with water, the excess of oxidant destroyed by sulphur dioxide, and the ketone extracted in the usual way.

Materials.—(i) *Ethanol.* A large reservoir of ethanol was prepared by diluting absolute ethanol with water to 99% by volume. This solvent was used for all kinetic measurements. The addition minimises possible errors due to variable traces of water.

(ii) *Benzaldehyde.* The aldehyde was washed with 10% aqueous sodium carbonate solution, dried ($CaCl_2$), and fractionated under reduced pressure in oxygen-free nitrogen. The pure aldehyde was stored in sealed ampoules under oxygen-free nitrogen. For each determination a fresh ampoule of benzaldehyde was employed.

[12] See, *e.g.*, Lutz and Jordan, *J. Amer. Chem. Soc.*, 1950, **72**, 4090; Kuhn, Lutz, and Bauer, *ibid.*, p. 5058; Black and Lutz, *ibid.*, 1955, **77**, 5134.
[13] Barnes, Barton, Fawcett, and Thomas, *J.*, 1952, 2339.
[14] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.

(iii) *Standard alkali.* The following procedure was found to be satisfactory for the storage of alcoholic potassium hydroxide. Approx. 0·15N-alcoholic potassium hydroxide was prepared by dissolving the requisite amount of the " AnalaR " reagent in freshly boiled-out 99% ethanol. The solution was filtered through sintered glass into a storage vessel in which the reagent could be kept under oxygen-free nitrogen and from which it could be delivered by applying an external pressure of the same gas. In spite of these precautions to exclude carbon dioxide during the filling of the storage vessel, a little potassium carbonate was always deposited during the first two days' storage; this did not, however, pass over with the alkali delivered from the storage vessel through the sintered-glass disc. The alkali was stored in the dark. It was standardised against potassium hydrogen phthalate in the usual way. For a rate determination exactly 0·1N-reagent was prepared by measuring the requisite volume of freshly boiled-out 99% ethanol into a volumetric flask and diluting it to the mark with alkali from the storage vessel. A fresh supply of standard alkali was prepared for every day's kinetic measurements. From Caldin and Long's results [15] it would not be expected that the addition of 1—2% of water to the 99% ethanolic solution would affect the concentration of ethoxide ion appreciably. This was confirmed by rate measurements, although any possible adventitious contamination with water is very much less than 1%.

(iv) *Benzylidene derivatives.* The following procedure was employed. The ketone (1 mol.) in 0·1M-potassium hydroxide in ethanol or dioxan–ethanol was treated with redistilled benzaldehyde (10 mols.) in a stoppered flask overnight at room temperature. The mixture was worked up in the usual way, the ethereal extract being washed, first, with saturated sodium metabisulphite to remove the excess of benzaldehyde. Removal of the solvent and recrystallisation of the residue, care being taken to avoid undue exposure to light, gave the required benzylidene derivatives.

The light-induced isomerisation of the normal benzylidene compounds was effected as follows. The benzylidene derivative in ethanol was irradiated with ultraviolet light. At suitable intervals aliquot parts were withdrawn and the absorption at 276 and 292 mμ measured. When the 276 mμ band no longer changed in intensity the alcohol was removed *in vacuo* and the residue recrystallised from the appropriate solvent. The " *iso*benzylidene " compounds were, in general, more insoluble and more easily crystallised than the normal derivatives.

(v) *Ketones.* Ketones required for this study were carefully purified to constant m. p. and rotation. These physical constants were, in general, in good agreement with those recorded in the literature. We report only on those preparations where special comment is required or where new compounds are involved.

Lanost-7-enone.—This was prepared by oxidation of lanost-7-en-3β-ol with pyridine–chromium trioxide. Chromatographed and then recrystallised from chloroform–methanol it had m. p. (plates) 144—146°, $[\alpha]_D$ −15° (*c* 2·04), and gave only a very weakly positive Zimmermann test. Lawrie, Hamilton, Spring, and Watson [9] record m. p. 146—147°, $[\alpha]_D$ −20° (*c* 2·8).

Lanosta-7 : 9(11)-dienone.—The derived *benzylidene* compound (needles from methanol) had m. p. 107—109°, $[\alpha]_D$ +9° (*c* 1·74), $\lambda_{max.}$ 236, 244, 252, 291 (ε 18,500, 20,800, 16,100, and 16,600 respectively) (Found: C, 86·25; H, 9·85. $C_{37}H_{52}O$ requires C, 86·65; H, 10·2%). Isomerisation with light gave the iso*benzylidene* compound (fine needles from methanol), m. p. 120—121°, $[\alpha]_D$ −72°, $\lambda_{max.}$ 236, 244, 252, 271 (ε 24,000, 24,500, 18,200, and 8,900 respectively) (Found: C, 86·85; H, 9·8%). Lanosta-7 : 9(11)-dienone itself had ε 18 at 292 mμ.

α-Amyr-12-ene-3 : 11-dione.—The derived *benzylidene* compound (needles from methanol) had m. p. 212—215°, $[\alpha]_D$ +51° (*c* 1·73), $\lambda_{max.}$ 232, 255, and 293 mμ (ε 12,400, 17,000, and 18,300 respectively) (Found: C, 84·35; H, 9·15. $C_{37}H_{50}O_2$ requires C, 84·35; H, 9·55%). This compound was also obtained by acid-catalysed condensation as follows. α-Amyr-12-ene-3 : 11-dione (160 mg.) in ethanolic hydrogen chloride (40 ml.; 34% w/w) was treated with redistilled benzaldehyde (0·57 ml.) at room temperature overnight. Working up in the usual way gave material identical with that described above. The parent ketone had ε <50 at 293 mμ.

β-Amyr-12-ene-3 : 11-dione.—The derived *benzylidene* compound (from methanol) had m. p. about 152° (decomp.), $[\alpha]_D$ +59° (*c* 2·05), $\lambda_{max.}$ 231, 255, and 294 mμ (ε 11,400, 16,300, and 18,100 respectively) after drying (Found: C, 82·0; H, 9·55. $C_{37}H_{50}O_2,CH_4O$ requires C, 81·65; H, 9·75%). The parent ketone had ε <50 at 294 mμ.

[15] Caldin and Long, *J.*, 1954, 3737.

β-*Amyra*-12 : 18-*diene*-3 : 11-*dione*.—3β-Hydroxy-β-amyra-12 : 18-dien-11-one [16] was oxidised at room temperature with pyridine–chromium trioxide overnight. Filtration of the product in benzene through alumina (Brockmann grade 2) and crystallisation from methanol afforded β-*amyra*-12 : 18-*diene*-3 : 11-*dione*, m. p. 214—216°, $[\alpha]_D$ +405° (*c* 1·12), $\lambda_{max.}$ 285 mμ (ε 12,700) (Found : C, 82·4; H, 9·9. $C_{30}H_{44}O_2$ requires C, 82·5; H, 10·15%). The ketone had absorption at 292 mμ (ε 11,400) which value was used in all runs for correcting the apparent ε value at 292 mμ.

Noroleana-16 : 18-*dienone*.—Oleanone (630 mg.) (prepared from morolic acid by Barton and Brooks's method [17]) in methylene dichloride (10 ml.) was treated with 0·62N-monoperphthalic acid (20 ml.) in ether, and the solution made up to 50 ml. with ether. After 17 hr. (1·04 mol. uptake of oxidant) the product was isolated, then taken up in methanol (100 ml.) and aqueous 2N-sulphuric acid (15 ml.) and refluxed for 30 min. Filtration of the product through alumina in benzene–light petroleum gave *noroleana*-16 : 18-*dienone* (from chloroform–methanol), m. p. 164—166°, $[\alpha]_D$ −14° (*c* 2·27), $\lambda_{max.}$ 240 mμ (ε 18,100) (Found : C, 85·4; H, 10·55. $C_{29}H_{44}O$ requires C, 85·25; H, 10·85%). This compound had ε <50 at 292 mμ.

Lanost-8-*enone*.—The derived *benzylidene* compound (needles from methanol) had m. p. 104—106°, $[\alpha]_D$ −22° (*c* 1·75), −19° (*c* 2·07), $\lambda_{max.}$ 292 mμ (ε 18,120 : mean determination) (Found : C, 86·15; H, 10·55. $C_{37}H_{54}O$ requires C, 86·3; H, 10·55%). Isomerisation by light afforded the iso*benzylidene* compound (from methanol), m. p. 110—111°, $[\alpha]_D$ +42° (*c* 1·87), $\lambda_{max.}$ 276 mμ (ε 8900) (Found : C, 86·2; H, 10·4%). The parent ketone had ε 36 at 292 mμ.

α-*Amyra*-9(11) : 12-*dienone*.—Oxidation of α-amyra-9(11) : 12-dienol with pyridine–chromium trioxide gave α-amyra-9(11) : 12-dienone (from methanol), m. p. 145—148°, $[\alpha]_D$ +414° (*c* 2·14 in pyridine), $\lambda_{max.}$ 281 mμ (ε 9600). The value of ε at λ 292 mμ was 8000. Widely different m. p.s are given in the literature for this compound but the rotations are in good agreement.[16, 19]

Noroleana-12 : 17-*dienone*.—Noroleana-16 : 18-dienone (see above) was isomerised with hydrogen chloride in chloroform according to Barton and Brooks's general method,[17] to give *noroleana*-12 : 17-*dienone*, m. p. 115—118°, $[\alpha]_D$ +118° (*c* 1·33), $\lambda_{max.}$ 236 and 243 mμ (ε 19,300 and 20,900 respectively) (Found : C, 84·85; H, 11·00. $C_{29}H_{44}O$ requires C, 85·25; H, 10·85%). The ketone had ε 170 at 292 mμ.

α-*Onoceradienedione*.—The derived *dibenzylidene* compound (needles from methanol) had m. p. 213—216°, $[\alpha]_D$ −37° (*c* 1·76 or 1·78), $\lambda_{max.}$ 225 and 292 mμ (ε 2 × 7600 and 2 × 17,900 respectively) (Found : C, 86·15; H, 8·6. $C_{44}H_{54}O_2$ requires C, 85·95; H, 8·85%). Isomerisation with light gave the iso*dibenzylidene* compound, fine needles (from chloroform–methanol), m. p. 223—224°, $[\alpha]_D$ −225° (*c* 1·51), $\lambda_{max.}$ 221 and 274 mμ (ε 2 × 14,100 and 2 × 8700 respectively) (Found : C, 85·75; H, 8·85%).

β-*Amyra*-11 : 13(18)-*dienone*.—Prepared by oxidation of the corresponding alcohol with pyridine–chromium trioxide, this ketone (from chloroform–methanol) had m. p. 241—242°, $[\alpha]_D$ −54° (*c* 1·75), $\lambda_{max.}$ 242, 250, and 260 mμ (ε 26,900, 30,400, and 19,600 respectively) (Found : C, 84·85; H, 11·25. Calc. for $C_{30}H_{46}O$: C, 85·25; H, 10·95%). Shaw, Spring, and Stevenson [19] record m. p. 236—240°, $[\alpha]_D$ −49°. The ketone had ε 42 at 292 mμ.

Methyl iso*Dehydro-oleanonate*.—Methyl *iso*dehydro-oleanolate [17] was oxidised with pyridine–chromium trioxide to give *methyl* iso*dehydro-oleanonate*, needles (from aqueous methanol), m. p. 153—154°, $[\alpha]_D$ +237°, $\lambda_{max.}$ 232 mμ (ε 7500) (Found : C, 79·9; H, 9·7. $C_{31}H_{46}O_3$ requires C, 79·8; H, 9·95%). The ketone had ε 60 at 292 mμ.

Methyl Dehydro-oleanonate.—Methyl dehydro-oleanolate, prepared from morolic acid by Barton and Brooks's method,[17] was oxidised with pyridine–chromium trioxide, to give *methyl dehydro-oleanonate* (from methanol), m. p. 186—187°, $[\alpha]_D$ −130° (*c* 1·44), $\lambda_{max.}$ 243, 251, and 260 mμ (ε 26,100, 29,500, and 18,500 respectively) (Found : C, 79·95; H, 9·7. $C_{31}H_{46}O_3$ requires C, 79·8; H, 9·95%). The ketone had ε 31 at 292 mμ.

α-*Amyr*-9(11)-*ene*-3 : 12-*dione*.—3β-Hydroxy-α-amyr-9(11)-ene-12-one [20] was oxidised with pyridine–chromium trioxide at room temperature overnight, to furnish α-*amyr*-9(11)-*ene*-3 : 12-*dione*, m. p. (from methanol) 192—194°, $[\alpha]_D$ +91° (*c* 1·80), $\lambda_{max.}$ 248 mμ (ε 11,000) (Found : C, 82·3; H, 10·25. $C_{30}H_{46}O_2$ requires C, 82·15; H, 10·55%). The ketone had ε 86 at 292 mμ.

[16] Picard and Spring, *J.*, 1941, 35.
[17] Barton and Brooks, *J.*, 1951, 257.
[18] Jacobs and Fleck, *J. Biol. Chem.*, 1930, **88**, 137.
[19] Shaw, Spring, and Stevenson, *J.*, 1956, 465.
[20] Seymour, Sharples, and Spring, *J.*, 1939, 1075.

β-*Amyr*-9(11)-*ene*-3 : 12-*dione*.—3β-Hydroxy-β-amyr-9(11)-ene-12-one [21] was oxidised with pyridine–chromium trioxide at room temperature for 7 hr., to give β-*amyr*-9(11)-*ene*-3 : 12-*dione*, needles (from methanol), m. p. 205—206°, $[\alpha]_D$ +52° (*c* 1·34), $\lambda_{max.}$ 248 mμ (ε 9500) (Found : C, 82·2; H, 10·45. $C_{30}H_{46}O_2$ requires C, 82·15; H, 10·55%).

β-*Amyra*-9(11) : 13(18)-*diene*-3 : 12 : 19-*trione*.—The corresponding alcohol [22] was oxidised with pyridine–chromium trioxide for 4 hr. at room temperature, to furnish β-*amyra*-9(11) : 13(18)-*diene*-3 : 12 : 19-*trione*, m. p. (from aqueous methanol) 289—291° (decomp.), $[\alpha]_D$ −96° (*c* 1·58), $\lambda_{max.}$ 277 mμ (ε 11,600) (Found : C, 80·35; H, 9·25. $C_{30}H_{42}O_3$ requires C, 79·95; H, 9·4%). The ketone had ε 9900 at 292 mμ.

Stability of Methyl Esters to Base.—In runs involving the use of methyl esters it was important to establish that the results were not vitiated through reduction in the concentration of base by hydrolysis of the ester. Such a possibility with oleanolic acid derivatives can at once be rejected (see Ruzicka, Furter, and van der Sluys-Veer [23]). The following experiment showed that hydrolysis was not significant in the experiments with methyl masticadienonate. The ester (18·7 mg.) in ethanolic 0·1N-potassium hydroxide (10 ml.) was kept at 25° for 7 hr. The solution was just acidified with dilute hydrochloric acid and extracted with ether. The dried (Na_2SO_4) ethereal solution was evaporated to dryness and the residue analysed (Found : OMe, 5·5. Calc. for $C_{30}H_{46}O_3$: 1OMe, 6·6%).

Absorption Measurements.—In order to correct for any day-to-day variation in the behaviour of the Unicam S.P. 500 spectrophotometer an absorption standard was prepared, consisting of pure naphthalene in ethanol (96%) measured against a blank of the same solvent. The intensities of the minimum at 284 mμ and the maximum at 266 mμ were determined with the same pair of stoppered 1 cm. cells on each occasion. No variation in the position of the maximum and minimum was ever observed (check on the wavelength scale). When variations in intensity were noted, both the maximum and minimum changed simultaneously. Such changes were generally less than 1%, but occasionally larger discrepancies were noted which must be ascribed to variation in the instrument. Measurements of the naphthalene solution on a particular day were taken as a standard value. The instrument was checked against this standard before each series of kinetic runs and, if instrument variation was detected, a proportional correction was applied to all measurements.

Technique.—Kinetic runs were made as follows. 10—20 mg. of the ketone were weighed (semimicro-balance) into a 10 ml. graduated flask. About 4 ml. of freshly prepared exactly 0·1N-ethanolic potassium hydroxide (see above) were added and the ketone was dissolved (if necessary with gentle warming). An ampoule of benzaldehyde (see above) was opened and about 300 mg. (~10 mols.) weighed into a 25 ml. volumetric flask and made up to the mark with the ethanolic 0·1N-potassium hydroxide. A portion (5 ml.) was pipetted into the ketone solution, and the mixture rapidly made up to the mark with the ethanolic potassium hydroxide, the time being noted. All solutions were kept at thermostat temperature (25·0°) until thermally equilibrated before being mixed. An identical control was prepared (without the ketone).

At suitable intervals aliquot parts (1 ml.) of both control and test solution were withdrawn and diluted at once to 10 ml. (volumetric flask) with 96% ethanol. The absorption of the test solution was measured at 292 mμ against the blank solution, 1 mm. quartz cells being used. It was established by prior experiment that this dilution technique effectively quenched the reaction during the time required to make measurements. Measurements were made at the benzylidene maximum of 292 mμ except where otherwise stated.

The stability of the control solution was examined and shown to vary only slightly with time (at zero time, at 292 mμ, ε 945, after 3 hr. ε 965, and after 70 hr. ε 1134). Clearly, however, the concentration of benzaldehyde diminishes by one molar proportion as the reaction proceeds. By measurement of the absorption spectrum of benzaldehyde at 292 mμ it was a simple matter to correct the observed intensities for this effect. The correction was, of course, in any case small.

The absorption of all compounds at 292 mμ was determined separately and, if significant, an appropriate correction to the observed ε at this wavelength was made for each kinetic observation. All calculations were referred to a maximum absorption at 292 mμ of 18,100. This value was established by careful measurements on the benzylidene derivative of lanost-8-enone

[21] Pickard, Sharples, and Spring, *J.*, 1939, 1045.
[22] Ruzicka and Jeger, *Helv. Chim. Acta*, 1941, **24**, 1236.
[23] Ruzicka, Furter, and van der Sluys-Veer, *ibid.*, 1938, **21**, 1735

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and shown to apply to several analogous benzylidene compounds (see above). The observations gave first-order plots from which the appropriate values of k were calculated and corrected for any slight variation in the 10 : 1 ratio of benzaldehyde to ketone. As emphasised in the text *all* experiments were run in pairs, one flask containing the standard lanost-8-enone, the other the ketone under examination. Expressing the results as the ratio of the two rates cancels any day-to-day variation in unforeseen factors. For ethanolic 0·1N-potassium hydroxide the mean rate constant for lanost-8-enone (106 runs) was $7{\cdot}78 \times 10^{-4}$ mole^{-1} l. sec.$^{-1}$ at 25·0° with error limits (calculated from the formula $\sqrt{\{\sum\Delta^2/[n(n-1)]\}}$, where the symbols have their usual significance) of $\pm 0{\cdot}05$.

In preliminary experiments it was shown that three-fold variation in the benzaldehyde concentration had little effect (see annexed Table) on the rate constant calculated as above. Since the variations in the benzaldehyde : ketone ratio were, in fact, minor, the small corrections applied (second-order kinetics being assumed) are undoubtedly justified.

Lanost-8-enone (mole l.$^{-1}$)	Benzaldehyde (mole l.$^{-1}$)	10^4k (sec.$^{-1}$)	10^4k/[Ph·CHO] (mole^{-1} l. sec.$^{-1}$)
0·00258	0·0306	2·43	7·94
0·00248	0·0521	4·36	8·36
0·00237	0·0994	8·01	8·07

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182. *Electrophilic Substitution. Part IX.* The Anomalous Nitrations of Quinoline.*

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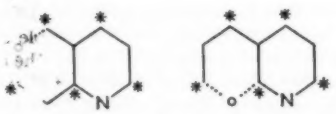
Quinoline has been observed to be nitrated in the 3-, 6-, and 8-position under certain conditions, and an explanation of this anomaly is offered. The nitration with pernitrous acid to give 5-, 6-, 7-, and 8-nitroquinolines is also discussed.

Electrophilic substitution in heterocyclic systems [1] is governed by (*a*) the relative ease of substitution of the different positions in the corresponding hydrocarbon and (*b*) the effect of the heterocyclic atom. In quinoline effects due to (*a*) should favour substitution, as in naphthalene, at α-positions, *i.e.*, at position 4, 5, or 8. The effect of the ring-nitrogen atom in electrophilic substitution should be two-fold : it should strongly deactivate the *Py*-ring and only favour substitution when the nitrogen occupies an unstarred position in the transition state, as shown :



One would therefore expect substitution in the 5-, 6-, and 8-positions in quinoline, the relative amounts depending on the magnitude of the various effects; and in fact nitration of quinoline in sulphuric acid gives a mixture of 5- and 8-nitroquinoline. Nevertheless nitrations of quinoline have been reported in which 7-nitroquinoline was stated to be the main product. Bacharach, Haut, and Caroline [2] reported that heating quinoline with lithium nitrate, copper nitrate, and acetic anhydride gave 7-nitroquinoline; Schorigin and

* Part VIII, *J.*, 1957, 345.

[1] Cf. Dewar, "Progress in Organic Chemistry," Butterworths, London, 1953, p. 21.
[2] Bacharach, Haut, and Caroline, *Rec. Trav. chim.*, 1933, **52**, 413.

Toptchiev [3] obtained the same material (together with a substance, m. p. 170—180°, which they suspected of being the 5 : 7-dinitroquinoline) by dripping nitrogen dioxide on hot quinoline. Laville and Waters,[4] investigating the action of pernitrous acid on quinoline, isolated 6- and 7-nitroquinilines in roughly equal amounts. These reactions needed further investigation, for they seemed contrary to existing theory.

Experimental

Materials.—The quinoline used was Hopkin and Williams's puriss. grade, which had been redistilled under a vacuum and stored over alumina. With one exception (as mentioned) the nitric acid used was of *d* 1·5. Spectra were measured in spectroscopically pure *cyclo*hexane on a Unicam S.P. 500 spectrophotometer. 5- and 7-Nitroquinoline used as reference compounds were synthesised by Bradford, Elliot, and Rowe's method; [5] commercial specimens of the 6- and 8-nitroquinoline were crystallised and sublimed *in vacuo* to constant m.p. Except where stated otherwise, the light petroleum used had b. p. 40—60°. Aqueous ammonia (*d* 0·880) was used for neutralising acid solutions.

Analytical Methods.—Chromatography proved unsuitable for quantitative analysis of mixtures of mononitroquinolines; however preliminary chromatography with benzene–light petroleum (b. p. 60—80°) on alumina was used to separate mixtures of quinoline with mononitroquinolines from the crude products. Quinoline was then removed by partial basification, the mononitroquinolines being extracted from a weakly acid solution (pH 2·1) with chloroform. Any 3-nitroquinoline was separated by virtue of its insolubility in N-hydrochloric acid. The detailed procedure used and the efficiency of the method are indicated by the following experiment with an artificial mixture.

3-Nitroquinoline (880 mg.), 6-nitroquinoline (59 mg.), 8-nitroquinoline (59 mg.), and quinoline (7·39 g.) were dissolved in acetic anhydride (100 ml.), hydrolysed with ice and water, and neutralised to litmus with ammonia. The volume of liquid was about 600 ml. This solution was extracted with chloroform (5 × 200 ml.), and the aqueous solution then discarded. The chloroform solution was next extracted with N-hydrochloric acid (4 × 200 ml.); the *Bz*-nitroquinolines and quinoline passed into the aqueous layer. The chloroform solution was then dried (Na_2SO_4) and filtered and the solvent distilled off. The residue, fraction I (3-nitroquinoline), a pale yellow solid (840 mg., 95%), had m. p. (crude) 121—125°; after one crystallisation it had m. p. 129—130°.

The acid solution was then basified to pH 2·2 and extracted with chloroform (4 × 150 ml.), giving fraction II in the chloroform layer. Since a mixture of chloroform and quinoline is hard to separate, the aqueous solution was washed with ether (2 × 50 ml.), then neutralised with ammonia and extracted with ether (5 × 200 ml.); this on drying (Na_2SO_4) and evaporation gave fraction III (quinoline; 6·35 g., 86%).

The chloroform solution containing fraction II was then evaporated to give a small amount of oil, smelling somewhat of quinoline. This was again dissolved in N-hydrochloric acid (100 ml.), partially basified to pH 2·2, and extracted with chloroform (4 × 50 ml.). The chloroform solution was dried and the solvent distilled off, to give fraction II, a quinoline-free oil which slowly crystallised (121 mg.; 102% recovery; contains some 3-nitroquinoline).

Thus the recovery of both the 3-nitroquinoline and of the 6- + 8-nitroquinoline fraction is virtually quantitative. However, owing to the considerable solubility of quinoline in water, the amount of quinoline recovered is only a rough guide to the amount present.

Nitrations.—The results quoted are for a selection of typical experiments.

*N.***1.** *Reaction between quinoline and metal nitrates in acetic anhydride.* A mixture of lithium nitrate (anhyd.; 12 g.), copper nitrate (0·2 g.), and quinoline (10 g.) was dissolved as far as possible in acetic anhydride (100 ml.). This was heated on a steam-bath for 1 hr. under reflux (until the evolution of nitrous fumes ceased). The solution was then cooled, hydrolysed with ice and water, and neutralised with ammonia. On extraction of a solution at pH 2·1 with chloroform and purification of the resultant nitroquinoline fraction, a pale yellow solid was obtained. This was crystallised from light petroleum–ether and from alcohol–water, yielding three substances. The major product, " X," had m. p. 130—131° and gave correct analyses for a

[3] Schorigin and Toptchiev, *Ber.*, 1936, **69**, 1874.
[4] Laville and Waters, *J.*, 1954, 400.
[5] Bradford, Elliot, and Rowe, *J.*, 1947, 442.

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mononitroquinoline (Found: C, 62·2; H, 3·6; N, 16·2. Calc. for $C_9H_6O_2N_2$: C, 62·0; H, 3·5; N, 16·1%) but depressed the m. p. of synthetic 7-nitroquinoline (m. p. 135—136°) to 110—125°. It formed a picrate, m. p. 162—163°, whereas the picrate of 7-nitroquinoline had m. p. 217—218°. The ultraviolet spectra were also different; 7-nitroquinoline had peaks at (log ε values in parentheses) 248 (4·37), 256·5 (4·3), and a plateau at about 284 mμ (3·97); "X" had peaks at 242·5 (4·45) and 295 mμ (4·0). 3-Nitroquinoline, prepared by Colonna's method,[6] had properties identical with those of "X" and did not depress its m. p. in admixture.

Material in the mother-liquors from "X" crystallised from light petroleum–ether to give, first, needles, m. p. 146—148° (raised to 151—152° on admixture with 6-nitroquinoline), and then needles, m. p. 89—90° (mixed m. p. with synthetic 8-nitroquinoline 90°).

N.2—6. *Nitrations with nitric acid–acetic anhydride.* These experiments were carried out under similar conditions. In N.2—5 quinoline (10 g.), acetic anhydride (120 c.c.), and nitric acid were heated at 100° for 1 hr. Experiment N.4 differed from N.3 only in that glass wool (10 g.) was added. In N.6, a solution of fuming nitric acid (7 ml.) in acetic anhydride (200 ml.) was added dropwise to the quinoline–acetic anhydride mixture during 7 hr. at 85—90°. The products were separated as previously described and fraction II was fractionally crystallised. The results are shown in Table 1.

TABLE 1.

Expt.	HNO_3 (ml.)	Yield (%) of nitroquinolines 3-	(6 + 8)-	Quinoline recovered (%)
N.2	3	1·9	0·8	55
N.3	5	6·6	0·9	—
N.4	5	6·2	0·7	—
N.5	7	3·8	0·9	47
N.6	7	6·2	0·7	14

N.7—9. *Reactions with nitrogen dioxide.* The nitration with nitrogen dioxide was repeated according to Schorigin and Toptchiev's method,[3] except that the nitrogen dioxide was not dropped on the hot quinoline as described but a current of the gas was bubbled through the quinoline. Nitrogen dioxide, made by heating lead nitrate in a steel tube, was dried by passage over phosphoric oxide and condensed in a small cooled flask. A stream of the gas mixed with air was bubbled through a pool of quinoline (25 g.) in the bottom of a 3-necked flask. A filter-pump at one end of the system of traps and condensers connected to one neck of the flask slowly drew the gases through the system. Three experiments were run, about 30—35 g. of nitrogen dioxide being used each time. The durations of the experiments were varied by bubling the gases through at different rates. Finally, the whole apparatus was washed out with 17% hydrochloric acid and chloroform. These solutions were then worked up as usual. Results were as in Table 2.

TABLE 2.

Expt.	Time of expt. (hr.)	Yields (%) of nitroquinolines 3-	(6 + 8)-	Quinoline recovered (%)
N.7	0·75	0·5	—	54
N.8	1·5	1·5	—	75
N.9	3·0	2·8	0·8	—

Nitration at the b. p. of quinoline gave the same products as well as a considerable amount of quinoline nitrate. No dinitro-compound could be isolated.

Miscellaneous Reactions.—*N*.10. Nitrogen dioxide was bubbled through a solution of quinoline in acetic anhydride (4 g. in 80 ml.) for 2½ hr. at 25°. This gave 200 mg. of 3-nitroquinoline but no 6- or 8-nitroquinoline.

N.11. A solution of quinoline (10 g.) in acetic anhydride (100 ml.) and nitric acid (*d* 1·42; 10 ml.) was left at *ca.* 20° for 5 months. It gave only 508 mg. of 3-nitroquinoline, and no 6- or 8-isomer.

N.12. Quinoline (1·1 g.) was dissolved in trifluoroacetic anhydride[7] (13 ml.) and trifluoroacetic acid (1 ml.). Nitric acid (0·7 ml.) was added and the solution was left at room temperature for 42 hr., after which the excess of anhydride was distilled off under reduced pressure and

[6] Colonna, *Boll. Sci. Fac. Chim. ind. Bologna*, 1941, 91.
[7] Bourne, Stacey, Tatlow, and Tedder, *J.*, 1949, 2977.

the residue hydrolysed. Working this up gave 170 mg. of crystals in fraction II and none in fraction I. Fraction II was then crystallised from ether–light petroleum to give, first, needles, m. p. 90—120° (which recrystallised from hot water in long needles, m. p. 150—152°, mixed m. p. with 6-nitroquinoline 151—152°); the mother-liquors then gave fine needles which on recrystallisation had m. p. 86—88° (mixed m. p. with 8-nitroquinoline, 88—89°). No other isomers could be detected.

N.13. Nitric oxide, made by dripping sulphuric acid (50%) on potassium iodide (34 g.) and sodium nitrite (14 g.) in water (50 ml.), was bubbled through a solution of quinoline (2·5 g.) in acetic anhydride during 1·5 hr. Fraction I contained 31 mg. of white solid, crystallising in needles, m. p. 162—163° from alcohol (Found: C, 57·2; H, 3·2; N, 22·1. $C_9H_5O_2N_3$ requires C, 57·7; H, 2·7; N, 22·5%). Thus the compound has the composition of a *dinitrosoquinoline*. It was also occasionally formed in reactions of type N.10, presumably owing to the use of impure nitrogen dioxide. If this reaction is carried out with gas containing a high proportion of dinitrogen trioxide, then only 3-nitroquioline is formed (as in N.10).

This " dinitrosoquinoline " has absorption max. (log ε in parentheses) at 226 (4·0), 262 (4·3), and 347·5 mμ (3·75).

Nitrations with pernitrous acid. Since Laville and Waters[4] reported recovery of large quantities of quinoline we used only one-fifth of their amount of quinoline while keeping the amounts of the other reactants constant. Quinoline (20 g.) was dissolved in sulphuric acid (2 ml.), acetic acid (3 ml.), and water (16 ml.) at 0°. Solutions were made up containing (i) sodium nitrite (48 g.) in water (140 ml.) and (ii) 100-vol. hydrogen peroxide (120 ml.) in sulphuric acid (3 ml.) and water (20 ml.). These two solutions were dripped separately into the base–acid mixture with stirring during 2 hr. No material was obtained in fraction I. After chromatography, fraction II was obtained as a pale yellow solid of low m. p.; about 6·4 g. of quinoline were recovered. In several runs, yields of fraction II varied from 1·7 to 3·4 g.

Fraction II (2·1 g.) was separated into three parts: (A) (600 mg.; m. p. 105—130°) by crystallisation from ether; (B) (250 mg.; m. p. 78—100°) by addition of light petroleum to the mother-liquors from (A); and (C) (1·11 g.) by evaporation of the remaining solution.

Fraction (A) crystallised from ether–light petroleum or alcohol–water in needles, m. p. 151—152°, undepressed on admixture with 6-nitroquinoline. Fractional crystallisation of (B) from ether–light petroleum gave a small amount of 6-nitroquinoline; the mother-liquors gave 7-nitroquinoline, m. p. 131—132°, raised to 132—133° on admixture with 7-nitroquinoline (admixture with 3-nitroquinoline lowered the m. p. sharply).

From part of the oil (C) a small amount of 8-nitroquinoline, m. p. and mixed m. p. 90—90·5°, separated. Further crystallisation of the mother-liquors yielded only a small amount of solid, m. p. *ca.* 50°, which was not raised by recrystallisation. This was probably the eutectic of 5- and 8-nitroquinoline described by Dufton.[5] The remainder of the oil (C) (330 mg.) was reduced in acetic acid (10 ml.) by iron powder (200 mg.) at the b. p. for 6 min. It was then poured into water, neutralised, and extracted with chloroform (3 × 150 ml.). The chloroform solution was dried and gave a brown oil on evaporation. This was extracted with boiling light petroleum (10 × 10 ml.), to give 173 mg. of light yellow oil. On careful crystallisation from light petroleum needles were obtained which on recrystallisation had m. p. 108·5—109·5°. 5-Aminoquinoline made from 5-nitroquinoline by the same procedure had m. p. 109—110°; there was no change of m. p. on mixture of the two samples. The picrates had m. p. and mixed m. p. 214—215°.

The results are summarised in Table 3.

TABLE 3. *Summary of results.*

Reagent	Nitroquinolines formed			Reagent	Nitroquinolines formed			
$LiNO_3$–$Cu(NO_3)_2$–Ac_2O; 100°	3	6	8	N_2O_4–Ac_2O; 20°	3			
HNO_3–Ac_2O; 100°	3	6	8	HNO_3–$(F_3C{\cdot}CO)_2O$; 20°		6		8
HNO_3–Ac_2O; 20°	3			Pernitrous acid; 0°	5	6	7	8
N_2O_4; 100°	3	6	8	NO–Ac_2O; 20°	$C_9H_5O_2N_3$			

The common feature of these reactions is the low yield of product; indeed it is usually possible to recover 50—70% of the quinoline. No other products could be isolated from any of the reactions investigated, all by-products being intractable tars.

[5] Dufton, *J.*, 1892, **61**, 783.

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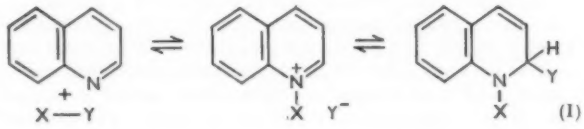
Discussion

(a) *Nitrations not involving Pernitrous Acid.*—The most surprising feature of these experiments was the isolation of 3-nitroquinoline as the major mononitration product; it seems clear that the material described previously by two independent groups of investigators as 7-nitroquinoline must in fact have been the 3-isomer as the melting points are very similar. We could not find any evidence for the formation of 7-nitroquinoline and were also unable to confirm the special virtue claimed for metal nitrates in acetic anhydride as nitrating agents; we obtained the same products, in rather better yield, by using equivalent amounts of nitric acid.

We consider that the formation of 3-nitroquinoline (and of the 6- and the 8-isomer), despite the small amount, is significant and presents an interesting theoretical problem since its formation is even more unexpected than would have been that of the 7-nitroquinoline. In the first place, 3-nitroquinoline would not be expected to be formed in detectable amount by direct nitration of quinoline; the reactivity of this position would not be expected to be greatly different from the 3-position in pyridine, the inertness of which to normal nitration is well known.[9]

We have also studied the rates of destruction of the *Bz*-mononitroquinolines when heated with a large excess (*ca.* 7 mols.) of nitric acid under the conditions of a typical nitration. The results show that the rates of destruction of the 5-, 6-, and 7-isomers were similar while that of the 8-isomer was rather less. Thus there is no reason to suppose that the 5-isomer, a major product of the straightforward nitration of quinoline in sulphuric acid, is formed here and then selectively destroyed by oxidation.

A likely mechanism for the reaction seems to be indicated by the fact that the only other isolable products were the 6- and the 8-isomer; indeed, with nitric acid in trifluoroacetic anhydride these alone could be isolated. This suggests that the entity being nitrated is not quinoline itself but a 1 : 2-dihydroquinoline derivative, formed by addition of the reagent to the 1 : 2-bond. This adduct (I) would be an aniline derivative and would be expected to be nitrated *ortho* and *para* to the nitrogen atom (*i.e.*, in the 6- and 8-position); while addition of oxides of nitrogen to the styrene-like double-bond of (I) followed by elimination could give the 3-isomer. It is interesting that the 3-nitroquinoline was formed only under conditions where oxides of nitrogen were present initially or could have been formed by reduction of nitric acid; in trifluoroacetic anhydride, a non-reducing solvent, only 6- and 8-nitroquinoline were formed.



(I)

The formation of adducts such as (I) is reasonable and there are many analogies;[10] similar intermediates (X = Bz; Y = CN) are postulated for the Reissert reaction. The nature of the reagent XY in our case is not clear, but we believe it to be an acyl nitrate (X = NO_2, Y = AcO, $CF_3 \cdot CO \cdot O$; or $\cdot NO_2$ in the case of nitrogen peroxide). We could obtain no evidence for a direct addition of acetic anhydride itself to quinoline; for example, the ultraviolet spectrum of quinoline in acetic anhydride is very similar to that in *cyclo*hexane. Kosower[11] has shown that an equilibrium exists between 1-methylpyridinium iodide and 1 : 2-dihydro-2-iodo-1-methylpyridine. We think it likely therefore, that

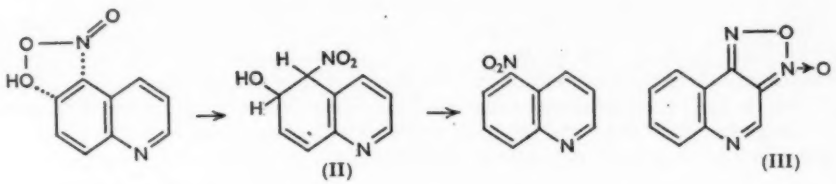
[9] den Hertog and Overhoff, *Rec. Trav. chim.*, 1930, **49**, 552.
[10] Doering and McEwen, *J. Amer. Chem. Soc.*, 1951, **73**, 2104; Gilman, Argersinger, and McEwen, *ibid.*, 1954, **76**, 41; Schofield and Simpson, *J.*, 1946, 472.
[11] Kosower, *J. Amer. Chem. Soc.*, 1955, **77**, 3883.

similar equilibria exist in other heterocyclic systems and that other polar molecules (*e.g.*, acetyl nitrate) can form similar adducts.

Experiments similar to those on quinoline were also carried out with *iso*quinoline and pyridine. In the former case only a small amount of intractable red tar was isolated, while nitration of pyridine in acetic anhydride and nitric acid at 100° gave a small amount (<1%) of 3-nitropyridine.[12]

It is possible that bromination of quinoline, by heating quinoline perbromide,[13] proceeds by an analogous though more efficient mechanism, addition of bromine to the intermediate (I; X = H, Y = Br) at the 3 : 4-bond being followed by elimination of two molecules of hydrogen bromide.

Nitration with Pernitrous Acid.—This clearly follows an entirely different path, since the products are quite different; unlike Laville and Waters,[4] we isolated comparable amounts of all four *Bz*-substituted isomers, but no 3-nitroquinoline was formed. Since in an experiment with nitrous acid under the same conditions there was no reaction whatever, and since free radicals would be expected to attack quinoline selectively in the 2-position (cf. high-temperature bromination [14]), it seems to us that the attacking entity must be pernitrous acid itself. Pernitrous acid may, like ozone, act as a double-bond reagent; ozone in fact selectively attacks the 5 : 6- and 7 : 8-bonds.[15]



(II) (III)

The intermediate (II) could undergo a variety of alternative elimination reactions, leading to phenols, etc.; this would account well for the copious formation of tarry and phenolic by-products.[16]

The " dinitrosoquinoline " isolated from the reaction of quinoline with nitric oxide may possibly have the structure of a quinolinofuroxan, *e.g.*, (III).

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[12] Dewar and Maitlis, *Chem. and Ind.*, 1955, 685.
[13] Claus and Collischon, *Ber.*, 1886, **19**, 2765.
[14] Jansen and Wibaut, *Rec. Trav. chim.*, 1937, **56**, 699.
[15] Wibaut and Boer, *ibid.*, 1955, **74**, 241.
[16] Cf. Halfpenny and Robinson, *J.*, 1952, 928, 939.

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183. *The Detection, by Means of Anthracene, of Free Radicals formed in "Abnormal" Reactions of Grignard Reagents.*

By R. O. C. Norman and William A. Waters.

Free alkyl and aryl radicals are produced from Grignard reagents under the catalytic action of cobaltous chloride in the presence of an organic halide, or on reaction with azobenzene. In both reactions, addition of radicals to anthracene has been observed. In ether, benzyl radicals add to give 9 : 10-dibenzyl-9 : 10-dihydroanthracene and three stereoisomers of 10 : 10′-dibenzyl-9 : 9′ : 10 : 10′-tetrahydro-9 : 9′-dianthryl; both phenyl and methyl radicals abstract hydrogen from the ether to give the radical ·CHMe·OEt which then adds to anthracene in a similar manner. In the reaction with azobenzene in benzene, addition of a methyl radical occurs to give one of the stereoisomers of 9 : 9′ : 10 : 10′-tetrahydro-10 : 10′-dimethyl-9 : 9′-dianthryl.

Although the majority of the reactions of Grignard reagents are heterolytic, many abnormal reactions are known in which fission of R·MgHal bonds is homolytic.[1,2] In their critical review Kharasch and Reinmuth [2] point out that the actual liberation of free radicals may not occur in all stages of these homolytic processes, and indeed diagnostic evidence of the liberation of free radicals from Grignard reagents is very scanty.

Since recent work in this laboratory [3,4,5] has shown how easily free radicals combine, even in dilute solution, with anthracene to give identifiable products, we have used this hydrocarbon to trap the free radicals that are liberated in two of the "abnormal" Grignard reactions, *viz.*, (*A*) their catalysed reactions with organic halides in the presence of a small percentage of a cobalt salt,[6] and (*B*) their reactions with azobenzene.[7,8,9]

Reaction *A* can now be represented as involving :

$$(1)\quad \mathrm{R{\cdot}MgHal} + \mathrm{CoCl_2} \longrightarrow \mathrm{R{\cdot}CoCl} + \mathrm{MgClHal}$$

$$(2)\quad \mathrm{R{\cdot}CoCl} \longrightarrow \mathrm{R\cdot} + \mathrm{\cdot CoCl}$$

$$(3)\quad \mathrm{\cdot CoCl} + \mathrm{R'Hal} \longrightarrow \mathrm{R'\cdot} + \mathrm{CoClHal}$$

and leads to the formation, in excellent yield, of dimers or disproportionation products of the organic radicals R· and R′·. There has however been much doubt whether reaction (2) really yielded *free* radicals R· and was not a bimolecular process (2*a* or *b*)

$$(2a)\quad \mathrm{2R{\cdot}CoCl} \longrightarrow \mathrm{R{\cdot}R} + \mathrm{2{\cdot}CoCl}$$

$$(2b)\quad \mathrm{2R{\cdot}CoCl} \longrightarrow \mathrm{R_{(+H)}} + \mathrm{R_{(-H)}} + \mathrm{2{\cdot}CoCl}$$

that gave only dimers or disproportionation products of the radical R·, for the early work of Kharasch and Fields [6,10] indicated that mixed dimers R·R′ did not seem to be formed in appreciable quantities. Thus the cobalt-catalysed reaction of phenylmagnesium bromide with *p*-tolyl bromide was reported to yield diphenyl and no methyldiphenyl, whilst the reaction of butylmagnesium bromide with bromobenzene gave only 3% of butylbenzene. It is now clear that with radicals of long life, such as benzyl, products R·R′ can be formed, for the cobalt bromide-catalysed reaction of benzylmagnesium

[1] Waters, "The Chemistry of Free Radicals," Clarendon Press, Oxford, 1946, pp. 211—214.
[2] Kharasch and Reinmuth, "Grignard Reactions of Non-metallic Substances," Prentice-Hall, New York, 1954, Chapter 5.
[3] Roitt and Waters, *J.*, 1952, 2695.
[4] Turner and Waters, *J.*, 1956, 879.
[5] Beckwith and Waters, *J.*, 1956, 1108.
[6] Kharasch and Fields, *J. Amer. Chem. Soc.*, 1941, **63**, 2316.
[7] Ref. 2, pp. 1249—1251.
[8] Gilman and Pickens, *J. Amer. Chem. Soc.*, 1925, **47**, 2407.
[9] Rheinboldt and Kirberg, *J. prakt. Chem.*, 1928, **118**, 1.
[10] Cf. Kharasch, Sayles, and Fields, *J. Amer. Chem. Soc.*, 1944, **66**, 482.

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bromide with ethyl bromide gives 20% of propylbenzene and 10% of dibenzyl.[11] Again Kharasch, Mulley, and Nudenberg,[12] investigating the addition of isoprene to the catalysed reaction between *iso*propylmagnesium bromide and 2-phenoxyethyl bromide, have isolated the coupled dimers $(PhO{\cdot}C_2H_4{\cdot}C_5H_8{\cdot})_2$ and $PhO{\cdot}C_2H_4{\cdot}[C_5H_8]_2{\cdot}CHMe_2$ in which the free radicals $Me_2CH{\cdot}$ and $PhO{\cdot}C_2H_4{\cdot}$ must have added independently to isoprene molecules.

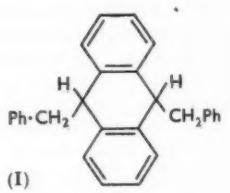
Undoubtedly ether, the customary solvent for Grignard reactions, is a very poor medium in which to attempt to detect an active radical such as methyl, butyl, or phenyl, for it is so easily dehydrogenated :

$$(4a)\quad Ph{\cdot} + \dot{C}H_3{\cdot}CH_2{\cdot}OEt \longrightarrow PhH + {\cdot}CHMe{\cdot}OEt$$

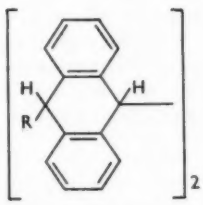
$$(4b)\quad Alk{\cdot} + CH_3{\cdot}CH_2{\cdot}OEt \longrightarrow AlkH + {\cdot}CHMe{\cdot}OEt$$

and since highly reactive Grignard reagents R·MgHal have usually been selected for effecting the conversion of halides R'Hal into dimers R'·R' the radical–solvent reactions (4), for which we have now obtained further diagnostic evidence (see below), probably account for failures to establish the independent existence of *free* radicals R· derived from the initial Grignard reagents.

In the present work the independent existence of the free benzyl radical has been established by isolating after reaction, from solutions that originally contained anthracene, a small but significant yield of 9 : 10-dibenzyl-9 : 10-dihydroanthracene (I), a trace of 9 : 10-dibenzylanthracene, and three forms of 10 : 10'-dibenzyl-9 : 9' : 10 : 10'-tetrahydro-9 : 9'-dianthryl (II; R = Ph·CH_2) which are probably geometrical isomers differing in their configurations at the *meso*-carbon atoms.



(I)



(II)

Two of these isomers have been synthesised by independent methods. Small quantities of anthraquinone were always isolated, but this may arise by photo-oxidation during the chromatographic separations. Compounds of type (I) are so easily dehydrogenated [13] that we suggest that the trace of dibenzylanthracene arises from compound (I) by dehydrogenation by the primary radicals, R·, R'·, present in the system and not by a direct substitution. The isolation of isomeric compounds of type (II) indicates that radicals such as benzyl must add individually to anthracene, and that at the low temperature of boiling ether their dimerisation to (II; R = Ph·CH_2) is not stereospecific. At the higher temperature of boiling toluene Beckwith and Waters [13] had isolated only the isomer (II), that of greatest thermal stability; into this each of the other isomers is converted when heated above its melting point.

All the anthracene derivatives mentioned above have been isolated after reaction in ether under nitrogen in presence of cobalt chloride between (i) benzylmagnesium chloride and benzyl chloride, (ii) benzylmagnesium chloride and butyl bromide (*i.e.*, R = Ph·CH_2, R' = Bu), and (iii) butylmagnesium bromide and benzyl chloride (*i.e.*, R = Bu, R' = Ph·CH_2). No such derivatives were obtained in ether solution in the absence of cobalt chloride. Reaction between anthracene, benzyl chloride, benzylmagnesium chloride, and cobalt chloride in boiling benzene gave 30% of 9 : 10-dibenzylanthracene

[11] Kharasch, Hancock, Nudenberg, and Tawney, *J. Org. Chem.*, 1956, **21**, 324.
[12] Kharasch, Mulley, and Nudenberg, *ibid.*, 1954, **19**, 1477.
[13] Beckwith and Waters, *J.*, 1956, in the press.

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and 14% of 9-benzylanthracene, as well as dibenzyl: from its entirely different character we suggest that this is mainly an aromatic substitution of the Friedel–Crafts type.

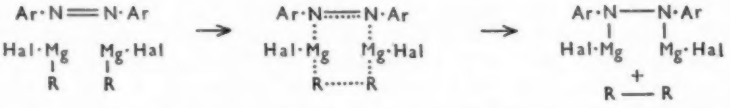
From the cobalt chloride-catalysed reactions, both of methylmagnesium iodide with methyl iodide and of phenylmagnesium bromide with phenyl bromide, there has been isolated a small amount of a dihydroanthracene derivative $(C_{18}H_{19}O)_2$ which we consider to be the dimer (II; R = ·CHMe·OEt) in which a 1-ethoxyethyl radical arising from reactions (*4a* and *4b*) has been added at a *meso*-position in anthracene.

Butylmagnesium bromide, cobalt chloride, and butyl bromide, however, gave disproportionation products and only a trace of an unidentified dihydroanthracene derivative.

The same technique has been used to detect the transient formation of free radicals in reactions between azobenzene and Grignard reagents:

$$(5)\quad \mathrm{Ph{\cdot}N{=}N{\cdot}Ph} + 2\mathrm{R{\cdot}MgHal} \longrightarrow \mathrm{HalMg{\cdot}NPh{\cdot}NPh{\cdot}MgHal} + 2\mathrm{R{\cdot}}$$

Here again Kharasch and Reinmuth [7] doubted whether *free* hydrocarbon radicals are involved and wrote the following reaction scheme to suggest that homolytic changes may be occurring within an addition complex:



When conducted under nitrogen in the presence of anthracene the reaction between azobenzene and benzylmagnesium chloride again yielded, besides hydrazobenzene and dibenzyl, compounds (I) and (II; R = $Ph{\cdot}CH_2{\cdot}$), so that free benzyl radicals had undoubtedly been generated. Similarly after reaction in benzene between azobenzene and methylmagnesium iodide one of the stereoisomers of 9 : 9′ : 10 : 10′-tetrahydro-10 : 10′-dimethyl-9 : 9′-dianthryl (II; R = Me) was isolated, but an attempt to isolate a corresponding product from the reaction between azobenzene and phenylmagnesium bromide failed.

Experimental

Materials.—Anthracene was purified by two distillations from ethylene glycol and had m. p. 217°.

Anhydrous cobaltous chloride was prepared from the hydrated material by distilling acetic anhydride over it and was dried at 130° in a vacuum.

Benzyl chloride, b. p. 178—179°, was purified by bubbling nitrogen through it to remove hydrogen chloride and then dried (K_2CO_3).

9-Benzylanthracene, prepared by Cook's method [14] from benzylideneanthrone and crystallised from ethanol, had m. p. 135°.

Chromatographic alumina used in the hydrocarbon separations was prepared by heating commercial alumina (Spence's alumina, type "H") at 700° for 4 hr., cooling it to 200°, and allowing it to cool to room temperature in a vacuum-desiccator. The light petroleum used in these separations had b. p. 60—80°.

Reactions were carried out in a steady stream of dry nitrogen, purified by passage through Fieser's solution.

(A) *Reactions of Grignard Reagents with an Organic Halide in the Presence of Cobaltous Chloride and Anthracene.*—The Grignard reagents were prepared from an excess of magnesium, and unchanged halide was destroyed by refluxing the solution for 2 hr. after visible reaction had ceased. The efficiency of the reaction was assumed to be 80% (cf. Kharasch and Reinmuth [15]). The ethereal solution of the reagent (1 equiv.), filtered under nitrogen from excess magnesium, was added dropwise during 8 hr. to a stirred refluxing solution of anthracene (0·25 equiv.) and an organic halide (1 equiv.) in ether in which was suspended a small amount (0·06 equiv.) of

[14] Cook, *J.*, 1926, 2160.
[15] Ref. 2, p. 30.

cobaltous chloride. After a further 8 hr. under reflux, the solution was cooled and the complex was decomposed with aqueous ammonium chloride. The product was washed with water and, when a benzyl or phenyl Grignard reagent or halide had been used, it was distilled in steam to remove dibenzyl or diphenyl. The product was extracted in ether, dried, and crystallised from light petroleum: unchanged anthracene was deposited and the mother-liquor was chromatographed.

In each case the structure of the product was proved by mixed m. p. and by infrared and ultraviolet spectra.

(a) *Reactions yielding benzyl radicals.* (i) The Grignard reagent formed from magnesium (5·0 g.) and benzyl chloride (21·0 g.) in ether (150 ml.) was added to anthracene (5·9 g., 1/30 mole) and benzyl chloride (16·7 g., 4/30 mole) in ether (500 ml.) in which was suspended cobaltous chloride (1·0 g.).

After reaction as described above, distillation in steam gave dibenzyl (3·90 g.), m. p. 52°. Crystallisation of the remainder of the product from light petroleum gave anthracene (1·87 g.). The mother-liquor was chromatographed: elution with light petroleum gave dibenzyl (0·15 g.) and then anthracene (1·85 g.); further elution with light petroleum–benzene (9 : 1) gave 9 : 10-dibenzyl-9 : 10-dihydroanthracene (0·67 g.), m. p. and mixed m. p. 119°. Elution with a 2 : 1 mixture of these solvents gave three isomers of 10 : 10′-dibenzyl-9 : 9′ : 10 : 10′-tetrahydro-9 : 9′-dianthryl which were separated by fractional crystallisation; the decreasing solubility of these compounds in methanol and ethanol corresponded with increasing m. p. [Found, (*a*) cpd. m. p. 238—240° (0·40 g.): C, 93·4; H, 6·5; (*b*) cpd. m. p. 227—229° (0·03 g.): C, 93·6; H, 6·3; (*c*) cpd. m. p. 182—183° (0·05 g.): C, 93·6; H, 6·4. $C_{42}H_{34}$ requires C, 93·7; H, 6·3%]. Substances (*a*) and (*c*) were synthesised by Beckwith and Waters,[13] but (*b*) is new. When (*b*) or (*c*) was heated in a sealed and evacuated tube above its m. p., it was converted into (*a*). The infrared spectra of these isomers show slight but significant differences.

Further elution gave 9 : 10-dibenzylanthracene (0·03 g.), m. p. 248°, and finally a small quantity of anthraquinone (10 mg.), m. p. 284°. Total significant recoveries were: anthracene, 63%; 9 : 10-dibenzyl-9 : 10-dihydroanthracene, 5·7%; 10 : 10′-dibenzyl-9 : 9′ : 10 : 10′-tetrahydro-9 : 9′-dianthryls, 5·5%; 9 : 10-dibenzylanthracene, 0·3%.

(ii) The reaction was repeated with *n*-butyl bromide (20·0 g.) in place of benzyl chloride. The products isolated were the same as those in (i) and in approximately the same proportions [unchanged anthracene 54·2%; (I) 5·4%; (II) 4·9%]. During the reaction a gas was evolved which decolorised bromine water and dilute alkaline permanganate solution.

(iii) Reaction (i) was repeated, with the Grignard reagent from *n*-butyl bromide (23·0 g.) and magnesium (5·0 g.) in ether (150 ml.) in place of benzylmagnesium chloride. The course of the reaction and the products were as in expt. (ii).

(iv) Reaction (i) was repeated, but the ethereal solution of the Grignard reagent was added to the other reactants in boiling benzene (500 ml.). Recrystallisation of the product from light petroleum gave 9 : 10-dibenzylanthracene (2·03 g.), m. p. 248°. Chromatography of the mother-liquor gave, successively in order, dibenzyl (3·01 g.), m. p. 52°, 9-benzylanthracene (1·26 g., 14·5%), m. p. 134°, anthracene (1·01 g., 17·1%), and 9 : 10-dibenzylanthracene (1·59 g.). The total yield of the last compound was 3·62 g. (30·7%).

(v) When the conditions of expt. (i) were applied in the absence of cobaltous chloride, no products from anthracene were obtained. Dibenzyl (45 mg.) was obtained by steam-distillation. Anthracene was recovered in 89% yield.

(b) *Reaction of butylmagnesium bromide with* n-*butyl bromide.* The conditions of expt. (i) above were applied to butylmagnesium bromide (from butyl bromide, 23·0 g., and magnesium, 5·0 g., in ether, 150 ml.) and butyl bromide (18·3 g.). A gas was evolved which contained ethylenic compounds. Anthracene was recovered in 72% yield and the only other product obtained by chromatography was a white compound (<10 mg.), m. p. 174—175°, whose ultraviolet spectrum was characteristic of dihydroanthracenes.

(c) *Reaction of methylmagnesium iodide with methyl iodide.* The conditions of expt. (i) were used in the reaction between methylmagnesium iodide (from methyl iodide, 23·0 g., and magnesium, 5 g., in ether, 150 ml.) and methyl iodide (18·5 g.). The total recovery of anthracene was 3·1 g. (52·5%). Elution of the alumina column with light petroleum–benzene (6 : 1) gave white cubic crystals (0·26 g.), m. p. 158° after recrystallisation from methanol [Found: C, 86·1; H, 7·9%; *M* (Cotterell's method in C_6H_6), 495. $(C_{18}H_{19}O)_2$ requires C, 86·1; H, 7·6%; *M*, 502]. Light absorption in EtOH: max. at 2650 Å (ε 1380). The infrared spectrum had

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strong bands at 8·92 and 9·25 μ (ether links) and in the 6—8 and 10—14 μ regions generally resembled dihydroanthracene derivatives. The compound was degraded to anthracene (i) by treatment of a solution in benzene with anhydrous aluminium chloride, (ii) by heating it with sulphur at 260° for 20 min., and (iii) by heating it with palladium–charcoal at 170° for 2 hr. This evidence is consistent with the formulation of this compound as 10 : 10′-*di*-(1-*ethoxyethyl*)-9 : 9′ : 10 : 10′-*tetrahydro*-9 : 9′-*dianthryl*.

Finally a small quantity of anthraquinone (15 mg.) was obtained.

(d) *Reaction of phenylmagnesium bromide with phenyl bromide.* When the conditions of expt. (i) were applied to phenylmagnesium bromide (from bromobenzene, 26·1 g., and magnesium, 5·0 g., in ether, 150 ml.) and bromobenzene (20·9 g.), there were isolated diphenyl (7·6 g.), m. p. 69°, and compound (II; R = CHMe·OEt) (0·30 g.), m. p. 158°.

(B) *Reaction of Grignard Reagents with Azobenzene.*—The technique was the same except that azobenzene (15·5 g.) was present in place of the organic halide and cobaltous chloride. Unchanged azobenzene was recovered by exhaustive distillation in steam, and hydrazobenzene was extracted in acid.

(a) *Reaction of benzylmagnesium chloride.* Unchanged azobenzene amounted to 40·6%, and hydrazobenzene, m. p. 130°, to 27%. Chromatography yielded (I) (4·7%) and (II) (R = Ph·CH_2) [isomers (*a*) and (*c*)] (4·2%), in addition to unchanged anthracene (60·5%).

(b) *Reaction of methylmagnesium iodide.* Benzene was added slowly to the ethereal Grignard reagent, and the solvent was distilled off until the reflux temperature was 79—80°. The resulting suspension of the Grignard reagent was added to the other components in benzene (500 ml.), and the reaction was carried out in the usual manner. Distillation in steam yielded azobenzene (43%), acid extraction gave hydrazobenzene (20%), and crystallisation and chromatography gave anthracene (70%) and one stereoisomer of 10 : 10′-*dimethyl*-9 : 9′ : 10 : 10′-*tetrahydro*-9 : 9′-*dianthryl* (1·5%), m. p. 213—214° after recrystallisation from ethanol (Found : C, 92·9; H, 6·8%; *M*, 310. $C_{30}H_{26}$ requires C, 93·3; H, 6·7%; *M*, 386). This was converted into the known isomer [5] by heating it in a sealed and evacuated tube above its m. p. Recrystallisation from ethanol gave the higher-melting isomer, m. p. and mixed m. p. 264°. Further elution gave anthraquinone (25 mg.) and left purple bands on the column which could not be eluted.

(C) *Reaction of phenylmagnesium bromide.* Reaction between phenylmagnesium bromide, azobenzene and anthracene in benzene, carried out as in the preceding case, gave no diphenyl. Unchanged anthracene was recovered in 41% and azobenzene in 24·3% yield. A considerable amount of tar was obtained, but after being boiled with concentrated hydrochloric acid this gave no material soluble in benzene. The organic material which was soluble in light petroleum–benzene was chromatographed, but apart from anthracene only oil was eluted, leaving intractable dark bands on the column.

We are grateful to Mr. A. L. J. Beckwith for specimens of 10 : 10′-dibenzyl-9 : 9′ : 10 : 10′-tetrahydro-9 : 9′-dianthryl, m. p. 252°, 9 : 10-dibenzyl-9 : 10-dihydroanthracene, m. p. 119°, 10 : 10′-dimethyl-9 : 9′ : 10 : 10′-tetrahydro-9 : 9′-dianthryl, m. p. 264°, and 9 : 10-dibenzylanthracene, m. p. 248°. One of us (R. O. C. N.) thanks the Department of Scientific and Industrial Research for a maintenance grant.

The Dyson Perrins Laboratory, Oxford. [*Received, August 3rd,* 1956.]

184. *Organosilicon Compounds. Part XX.* Medium Effects in the Reaction between Trimethylsilylmethylbenzoate Ions and Hydroxide Ion.*

By C. Eaborn and S. H. Parker.

The reaction between *o*-, *m*-, and *p*-trimethylsilylmethylbenzoate ions and alkali-metal hydroxides in water and in aqueous methanol has been studied kinetically over a wide range of ionic strength. Even at the high salt concentrations involved (up to 1M) the salt-effects are consistent with the Brönsted–Bjerrum theory for reaction between two negative ions.

We have studied the alkaline cleavage of *o*-, *m*-, and *p*-trimethylsilylmethylbenzoic acids in the hope of obtaining more information about the mechanism of cleavage of C–Si bonds. Whilst this hope was not realised, the results provide a picture of medium effects in reactions between ions at a time when the theory of these effects is under review.[1]

Salt Effects.—For all three isomers, increase in the concentration of sodium hydroxide causes marked increase in the specific rate constant, k_s (the observed first-order rate constant divided by the alkali concentration), as Table 1 shows.

Table 1. *Reactions in water at 49·7° of trimethylsilylmethylbenzoate ions.*

para-Ion [a]				*meta*-Ion [b]		*ortho*-Ion [b]	
[NaOH]	10^2k_s [c]	[NaOH]	10^2k_s [c]	[NaOH]	10^4k_s [c]	[NaOH]	10^4k_s [c]
0·983	6·80	0·102	4·43	1·025	6·99	1·025	12·0
0·788	6·30	0·0760	4·25	0·530	5·63	0·530	9·25
0·592	5·95	0·0525	3·91	0·282	4·70	0·282	7·28
0·396	5·48	0·0294	3·61	0·158	3·89	0·158	5·83
0·200	4·82	0·0150	3·35				

[a] $2·5 \times 10^{-3}$M. [b] $2·5 \times 10^{-2}$M. [c] In min.$^{-1}$ mole^{-1} l.

The values for the *para*-isomer extend to sufficiently low salt concentrations to provide a test of the Brönsted–Bjerrum theory of salt effects.[2] According to this the rate of a reaction between two ions, A and B, is given by $k = k_0 f_A f_B / f_\ddagger$, where k_0 is the rate constant at infinite dilution and f_A, f_B, and $f_\ddagger$ are the activity coefficients of A, B, and the transition state, respectively. The activity coefficient, f_i, of an ion, i, is given by $-\log f_i = Z_i^2 \alpha \mu^{\frac{1}{2}}/(1 + \beta d_i \mu^{\frac{1}{2}})$ where Z_i is the charge on the ion, d_i the distance of closest approach of another ion to the i-th ion, and β and α are constants (which for water at 49·7° have values of $0·334 \times 10^8$ and 0·503, respectively [3]). When $Z_A = Z_B = -1$, and the charge on the transition state is consequently -2, the reaction rate is given by

$$\log k = \log k_0 - \frac{\alpha\mu^{\frac{1}{2}}}{1 + \beta d_A \mu^{\frac{1}{2}}} - \frac{\alpha\mu^{\frac{1}{2}}}{1 + \beta d_B \mu^{\frac{1}{2}}} + \frac{4\alpha\mu^{\frac{1}{2}}}{1 + \beta d_\ddagger \mu^{\frac{1}{2}}} \quad . \quad . \quad . \quad (1)$$

and a mean value, d, being adopted for the distance of closest approach, $\log k = \log k_0 + 2\alpha\mu^{\frac{1}{2}}/(1 + \beta d\mu^{\frac{1}{2}})$.

As required, the variation in the rate of reaction, k_s, of the *para*-isomer with sodium hydroxide can be expressed by an equation, $\log k_s = \log k_0 + 1·06/(C + 1/\mu^{\frac{1}{2}})$, as shown by the fair constancy of $\log k_0$ [$= \log k_s - 1·06/(1·55 + 1/\mu^{\frac{1}{2}})$] in Table 2. The value of the constant C corresponds to the reasonable figure of 4·6 Å for the mean distance of closest approach of the ions. The success of this treatment indicates that there are no complications from ion-association even at the highest salt concentrations.

The rates of reaction of the *ortho*- and the *meta*-isomer increase more rapidly with

* Part XIX, *J.*, 1957, 498.

[1] Harty and Rollefson, *J. Amer. Chem. Soc.*, 1954, **76**, 4811, and references therein.

[2] Frost and Pearson, "Kinetics and Mechanism," John Wiley and Sons Inc., New York, 1953, p. 138.

[3] Robinson and Stokes, "Electrolyte Solutions," Butterworths Scientific Publications, London, 1955, pp. 228, 491.

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increasing alkali concentration than does that of the *para*-isomer. The data extend over a very limited range of concentration, but in both cases an equation of form $\log k_s = \log k_0 + 1{\cdot}06/(C + 1/\mu^{\frac{1}{2}})$ can be derived with moderate success, as Table 3 shows. The values for the mean distance of closest approach of the ions (1·8 and 2·4 Å, respectively, for the *ortho*- and the *meta*-isomer) are rather low.

TABLE 2.

10[NaOH]	9·83	7·88	5·92	3·96	2·00	1·02	0·760	0·525	0·294	0·150
10μ *	9·86	7·90	5·95	3·98	2·02	1·05	0·785	0·550	0·319	0·175
$-\log k_s$	1·167	1·20	1·225	1·26	1·32	1·35	1·37	1·41	1·44	1·47
$1{\cdot}06/(1{\cdot}55 + 1/\mu^{\frac{1}{2}})$	0·415	0·396	0·372	0·338	0·285	0·228	0·207	0·182	0·149	0·116
$-\log k_0$	1·58	1·60	1·60	1·60	1·58	1·58	1·59	1·59	1·59	1·59

* Includes the concentration of sodium *p*-trimethylsilylmethylbenzoate ($2{\cdot}5 \times 10^{-3}$M).

The results emphasise that in examining effects of structural change on the rate of reaction between ions, rate constants cannot safely be compared at a fixed ionic strength but must be extrapolated to infinite dilution. Thus the relative reactivities of the *para*- and the *ortho*-isomer above are 58 : 1 at a salt concentration of 1·05M, 85 : 1 at a salt concentration of 0·18M, and 100 : 1 at infinite dilution, the derived $\log k_0$ values being used.

TABLE 3.

	ortho-Ion				*meta*-Ion			
[NaOH]	1·025	0·530	0·282	0·158	1·025	0·530	0·282	0·158
μ *	1·050	0·555	0·307	0·183	1·050	0·555	0·307	0·183
$-\log k_s$	2·921	3·034	3·138	3·234	3·156	3·250	3·326	3·410
$1{\cdot}06/(C + 1/\mu^{\frac{1}{2}})$ [b]	0·672	0·555	0·443	0·363	0·594	0·500	0·407	0·338
$-\log k_0$	3·593	3·589	3·581	3·597	3·750	3·750	3·735	3·748

* Includes the concentration of the sodium salt of the organosilicon acid (0·025M). [b] $C = 0{\cdot}59$ and 0·80, respectively, for the *ortho*- and the *meta*-isomer.

Specific Salt Effects.—At high ionic strengths, salt effects frequently depend upon the nature as well as the concentration of the salts present.[1] In the reaction of the *p*-trimethylsilylmethylbenzoate ion, sodium chloride has a markedly smaller effect than sodium hydroxide. Thus at a sodium hydroxide concentration of 0·0294M the presence of 0·0614M-sodium chloride increases k_s (at 49·7°) from 3·6 to $4{\cdot}0 \times 10^{-2}$ min.$^{-1}$ mole^{-1} l. whereas in 0·0908M-sodium hydroxide k_s is *ca.* $4{\cdot}4 \times 10^{-2}$ min.$^{-1}$ mole^{-1} l. Again, in the presence of 0·833M-alkali and 0·491M-sodium chloride $k_s = 6{\cdot}6 \times 10^{-2}$ min.$^{-1}$ mole^{-1} l., whereas in 1·324M-alkali $k_s = ca.\ 7{\cdot}8 \times 10^{-2}$ min.$^{-1}$ mole^{-1} l. (by extrapolation).

TABLE 4. *Reaction of the* para*-ion and various alkalis in water* (49·7°).

10^2[NaOH]	98·3	78·8	59·2	39·2	20·0	10·2	7·60	5·25	2·94	1·50
10^2k_s (min.$^{-1}$ mole^{-1} l.)	6·80	6·30	5·95	5·48	4·82	4·43	4·25	3·91	3·61	3·35
* 10^2k_a (min.$^{-1}$ mole^{-1} l.)	10·22	9·28	8·67	7·86	6·62	5·76	5·38	4·77	4·17	3·72
10^2[KOH]	98·3	78·8	59·2	39·6	20·0	10·2	5·25			
10^2k_s (min.$^{-1}$ mole^{-1} l.)	7·70	6·96	6·57	5·76	4·97	4·64	4·12			
* 10^2k_a (min.$^{-1}$ mole^{-1} l.)	10·20	9·37	8·96	7·83	6·53	5·81	4·78			
10^2[LiOH]	106·3	85·1	63·9	42·7	21·5	10·9				
10^2k_s (min.$^{-1}$ mole^{-1} l.)	5·49	5·30	5·05	5·06	4·68	4·32				
* 10^2k_a (min.$^{-1}$ mole^{-1} l.)	9·97	9·34	8·55	8·00	6·71	5·74				

* Activity coefficients [4,5] at 25° have been used since those of lithium hydroxide are not known at higher temperatures.

A more interesting aspect of specific salt effects is revealed by the rates of reaction of the *p*-benzoate with sodium, lithium, and potassium hydroxides. The specific rates depend on which alkali is present, as Table 4 reveals; *e.g.*, at 1M-alkali the reaction with

[4] Harned and Swindells, *J. Amer. Chem. Soc.*, 1926, **48**, 126.
[5] Conway, " Electrochemical Data," Elsevier Publishing Co., 1952, pp. 87, 88.

potassium hydroxide is *ca.* 1·5 times as fast as that with lithium hydroxide. If the specific rates are referred to mean activities instead of concentrations of alkalis (*i.e.*, $k_a = k_s/f_{MOH}$, where f_{MOH} is the mean activity coefficient of the alkali) then the specific rates, k_a, at a particular alkali concentration are reasonably independent of which alkali is present.

Since, say, the first term on the right-hand side of equation (1) refers to variation of the activity coefficient of hydroxide ion with ionic strength, we have $\log k_a = \log k_0 + 3\alpha\mu^{\frac{1}{2}}/(1 + \beta d'\mu^{\frac{1}{2}})$ where d' is now the mean distance of closest approach of carboxylate ion and of the transition state, and would be expected to be rather larger than d, above, which includes the closest approach distance for hydroxide ion.

A plot of $\log k_a$ against $1/(C + 1/\mu^{\frac{1}{2}})$ (where $C = 1{\cdot}7$, corresponding to a mean distance of closest approach of the ions of 5·1 Å) is, as required, a straight line of slope 1·60 (*i.e.*, 3α), as revealed by the constancy of $\log k_0$ in Table 5; $\log k_0$ has the same value as when derived from specific rate constants, k_s, above. This plot covers all three alkalis, and it is thus clear that specific effects of the cations are exerted solely on the activity coefficient of the hydroxide ion, the ratio of the activity coefficients of the carboxylate ion and the transition state being independent of the nature of the cation.

TABLE 5.

		KOH		NaOH		LiOH			
	1·6					1·6			
[MOH]	$1{\cdot}7 + 1/\mu^{\frac{1}{2}}$	$-\log k_a$	$-\log k_0$	$-\log k_a$	$-\log k_0$	[MOH]	$1{\cdot}7 + 1/\mu^{\frac{1}{2}}$	$-\log k_a$	$-\log k_0$
0·983	0·592	0·993	1·585	0·991	1·583	1·063	0·600	1·000	1·600
0·788	0·566	1·028	1·594	1·033	1·599	0·851	0·576	1·030	1·606
0·592	0·534	1·048	1·582	1·062	1·596	0·639	0·523	1·068	1·591
0·396	0·486	1·106	1·592	1·105	1·591	0·427	0·494	1·097	1·591
0·200	0·408	1·185	1·593	1·179	1·587	0·215	0·416	1·173	1·589
0·102	0·334	1·236	1·570	1·255	1·589	0·109	0·339	1·241	1·580
0·0760	0·269	1·321	1·590	1·270	1·574	—	—	—	—
0·0525	—	—	—	1·321	1·590	—	—	—	—
0·0294	—	—	—	1·380	1·599	—	—	—	—
0·0150	—	—	—	1·429	1·602	—	—	—	—

Change of Solvent.—Equation (1) for salt effects can be applied with fair success to the cleavage of the *p*-carboxylate ion by sodium hydroxide in 5% (w/w) of water in methanol. (Most of the alkali will be present as methoxide ion.) In methanol at 50° (dielectric constant, 30·4) a plot of $\log k_s$ against $1/(C + 1/\mu^{\frac{1}{2}})$ should have a slope of 3·7. The values of $\log k_0$ derived from the equation $\log k_s = \log k_0 + 3{\cdot}7/(2{\cdot}8 + 1/\mu^{\frac{1}{2}})$ are reasonably constant as Table 6 shows. The value, 2·8, of C corresponds to a mean distance of closest

TABLE 6. *Cleavage of the* para-*ion in* 5% *(w/w) water–methanol* (49·7°).

[NaOH]	1·023	0·869	0·767	0·630	0·526	0·396	0·262	0·130
[a] $-\log k_s$	2·493	2·520	2·548	2·585	2·597	2·652	2·728	2·810
[b] $3{\cdot}7/(2{\cdot}8 + 1/\mu^{\frac{1}{2}})$	0·977	0·955	0·943	0·914	0·888	0·844	0·781	0·670
$-\log k_0$	3·470	3·475	3·491	3·499	3·485	3·496	3·509	3·480

[a] k_s in min.$^{-1}$ mole^{-1} l. [b] The concn. of sodium trimethylsilylmethylbenzoate ($2{\cdot}5 \times 10^{-3}$M) is taken into account.

approach of the ions of 5·5 Å (since $\beta = 0{\cdot}507 \times 10^8$) in good agreement with the figures of 4·5 Å for the reaction in aqueous solution where the alkali is all present as hydroxide ion. If the derived value of $\log k_0$ is correct then the presence of 1M-alkali causes a 10-fold rate increase in the specific rate constant.

The effect on k_s (at 49·7°) of change of solvent from water to 39% (w/w) of water in methanol is shown in Table 7 for all three isomers at the same sodium hydroxide concentration (0·98M), along with the accompanying changes in the energy and entropy factors of the Arrhenius equation. The rate is decreased in all three cases, more for the *meta*-compound than for the other two. (It is clear from the discussion above that the rate

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ratios would be substantially different at infinite dilution.) Such a decrease in rate on going to a less polar medium is expected for a reaction between ions of like charge.[7]

For uncharged benzyltrimethylsilanes increase in activation energy caused by structural change is accompanied by increase in the log A factor, while in the case of the carboxylate ions increase in E between *para*- and *ortho*- and *meta*-isomers is accompanied by decrease

TABLE 7.

Ion	*para*		*ortho*		*meta*	
Water (wt.-%)	100	39	100	39	100	39
10^4k_a (min.$^{-1}$ mole^{-1} l.)	680	94	11·9	1·39	6·9	0·59(5)
Rate ratio	7·2	1	8·6	1	11·6	1
E (kcal.)	19·6	20·6	21·2	22·4	21·9	22·9
log A *	12·05	12·15	11·45	11·3	11·7	11·3

* Based on time (min.).

in log A. This is because of direct interaction between the negative charges on the reactants,[7] which will be least important for the *para*-compound since the charges will be furthest apart in the transition state. This interaction, operating through both E and log A, along with the larger inductive effect from the *ortho*-position, is sufficient to account for the low reactivity of the *ortho*-compound compared with the *para*-isomer.

The Mechanism of the Cleavage.—The kinetics of the reactions between neutral benzyltrimethylsilanes and sodium hydroxide are consistent with either of the two mechanisms below, of which (*a*) involves synchronous attack of hydroxide ion and separation of the benzyl ion, and (*b*) initial formation of a quinquecovalent silicon intermediate.[6] (In both cases the benzyl anion will react rapidly with solvent.)

$$(a)\ HO^- + SiMe_3\cdot CH_2\cdot C_6H_4\cdot X \longrightarrow \underset{\text{(transition state)}}{HO\cdots SiMe_3\cdots CH_2\cdot C_6H_4\cdot X} \longrightarrow HO\cdot SiMe_3 + {}^-CH_2\cdot C_6H_4\cdot X$$

$$(b)\ HO^- + SiMe_3\cdot CH_2\cdot C_6H_4\cdot X \underset{(1)}{\overset{\text{fast}}{\rightleftharpoons}} HO\bar{S}iMe_3\cdot CH_2\cdot C_6H_4\cdot X \xrightarrow{\text{slow}} HO\cdot SiMe_3 + {}^-CH_2\cdot C_6H_4\cdot X$$

At first sight, when $X = CO_2^-$, the close agreement of the salt effects with those expected for reaction between two negative ions seem to rule out mechanism (*b*), since the rate-determining step in this involves a doubly-charged reactant and a doubly-charged transition state and will not be much affected by ionic-strength changes. However, the salt effects are determined by change from the original ground state (*i.e.*, separate negative ions) to this doubly-charged transition state, and thus will be the same in mechanisms (*b*) and (*a*). Similar conclusions can be reached by considering the effect on the overall rate of variation in the equilibrium constant of step (1) with ionic strength.

EXPERIMENTAL

For reactions in water the acids were dissolved in a slight excess of aqueous alkali and a suitable volume of this solution was added to more concentrated alkali to initiate reaction. The reactions were followed spectrophotometrically as previously described.[6]

UNIVERSITY COLLEGE, LEICESTER. [*Received, August 17th*, 1956.]

[6] Eaborn and Parker, *J.*, 1955, 126.
[7] Frost and Pearson, *op. cit.*, p. 133.

185. *Complexes involving Tervalent Iron and Orthophosphoric Acid. Part IV.* Evidence for the Formation of Polynuclear Complexes from Ion-exchange Experiments.*

By A. Holroyd and J. E. Salmon.

Cation-exchange studies of ferric sulphate–phosphoric acid solutions have provided evidence for the formation therein of polynuclear phosphatoferric cations and, possibly, when much free sulphuric acid is present, of polynuclear complex ions containing both phosphato- and sulphato-groups. Anion-exchange studies have also indicated the formation of mixed phosphato-sulphato-complexes.

The results of cation-exchange experiments with ferric chloride–phosphoric acid solutions are consistent with the sorption of polynuclear phosphatoferric cations from solutions containing little free hydrochloric acid and of the monomeric $FeHPO_4^+$ ion from solutions containing higher concentrations of free acid.

Previous papers in this series contained evidence of the formation of a cationic complex $FeHPO_4^+$ in solutions containing approximately equimolecular amounts of ferric chloride and phosphoric acid [1] and of anionic complexes such as $[Fe(HPO_4)_3]^{3-}$ or $[Fe(PO_4)_3]^{6-}$ in solutions of ferric phosphate in phosphoric acid.[2] Amongst the experimental facts quoted in support of the formation of the $FeHPO_4^+$ ion were the results of pH-titrations of ferric chloride solutions with phosphoric acid. However, recent studies [3] indicated that the release of hydrogen ions during the pH-titration is much less when ferric sulphate is substituted for ferric chloride. This might arise because the chloro-complexes of iron(III) are more labile than sulphato-complexes, and the chloro-groups are more easily displaced by phosphate than are the sulphate groups. A further cause might be found in the buffering action of the sulphate complexes, which would remove some of the hydrogen ions liberated: $FeSO_4^+ + H^+ \rightleftharpoons FeHSO_4^{2+}$. Nevertheless the difference between the two systems seemed sufficiently great to warrant examination of the ferric sulphate–phosphoric acid system by use of the ion-exchange methods described before.[1] In view of the unexpected results obtained, the previous work on the ferric chloride–phosphoric acid system was extended.

Experimental

Procedure.—The batch technique described by Salmon [4] was employed, with 50 ml. of solution and either 0·500 g. of cation exchange resin (Zeo-Karb 225) or 1·000 g. of anion exchange resin (I.R.A. 400). Hydrochloric acid or, in some cases, nitric acid (2N, *ca.* 300 ml.) was used to elute the species sorbed on the resin. The combined eluate and washings were made up to 500 ml. and aliquot portions used for analysis. As a check, aliquot samples of the solution in equilibrium with the resin were also analysed in most experiments. Equilibrium was reached in 3—4 days if frequent and prolonged agitation was employed, but generally at least a week was allowed.

Analysis.—Iron was determined by titration with potassium dichromate, after elimination of nitric acid, phosphate as phosphomolybdate, after elimination of hydrochloric acid (if present), and sulphate as barium sulphate, after removal of iron by sorption on a column of cation exchange resin. The capacity of the resin was determined as previously described.[1]

Reagents.—All reagents, apart from the ferric sulphate whose purity was checked, were of analytical grade.

* Part III, *J.*, 1954, 28.

[1] Salmon, *J.*, 1953, 2644.
[2] Jameson and Salmon, *J.*, 1954, 28.
[3] Holroyd and Salmon, *J.*, 1956, 269.
[4] Salmon, *Rev. Pure Appl. Chem.*, 1956, **6**, 24.

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Results and Discussion

The results of the cation-exchange experiments with mixtures in various proportions of ferric sulphate (0·1M in Fe) and phosphoric acid (0·3M) solutions are shown in Table 1, together with those of further experiments in which the pH of the ferric sulphate solution was

Table 1. *Sorption of iron and phosphate by Zeo-Karb* 225 (H-*form*, 0·500 *g.*) *from solutions* (50 *ml.*) *containing ferric sulphate and phosphoric acid.*

Solution		Resin						
$\frac{[PO_4]}{[Fe]}$	pH *	N_{Fe}	$N_{phosphate}$	q †	Possible complexes ‡	q for complexes	q (average)	$pN_{Fe} - qN_{phosphate}$
(1) Ferric sulphate solution, pH 1·34, $p = 3$.								
0·00	1·18	0·333	—	—	—	—	—	1·00
0·33	1·03	0·535	0·203	2·98	*a*	3	3	1·00
0·75	0·99	0·566	0·269	2·60	*a* or *d*	3 or 2	2·5	1·03
1·29	0·97	0·584	0·313	2·40	*a* or *d*	3 or 2	2·5	0·97
1·69	0·93	0·581	0·271	2·74	*a* or *d*	3 or 2	2·5	1·06
2·78	0·95	0·553	0·219	3·05	*a*	3	3	1·00
4·51	0·98	0·510	0·159	3·24	*a*	3	3	1·05
(2) Ferric sulphate solution, pH 1·15, $p = 3$ (assumed).								
0·41	0·98	0·480	0·163	2·70	*a* or *d*	3 or 2	2·5	1·03
0·75	0·95	0·498	0·193	2·56	*a* or *d*	3 or 2	2·5	1·01
0·95	0·94	0·507	0·215	2·42	*a* or *d*	3 or 2	2·5	0·98
1·69	0·96	0·518	0·232	2·39	*a* or *d*	3 or 2	2·5	0·98
(3) Ferric sulphate solution, pH 0·98, $p = 3$ (assumed).								
0·00	0·94	0·319	—	—	—	—	—	0·96
0·40	0·81	0·461	0·106	3·62	*a* or *e*	3 or 4	3·5	1·01
0·74	0·80	0·477	0·124	3·48	*a* or *e*	3 or 4	3·5	1·00
0·93	0·80	0·484	0·133	3·40	*a* or *e*	3 or 4	3·5	0·99
1·66	0·83	0·487	0·156	2·95	*a*	3	3	0·99

* Of solution in equilibrium with resin.
† $q = (pN_{Fe} - 1)/N_{phosphate}$.
‡ $a = Fe_2(PO_4)^{3+}$; $b = Fe_2(PO_4)(OH)^{2+}$; $c = Fe_2(PO_4)(OH)_2^{+}$; $d = FeHPO_4^{+}$; $e = Fe_2(PO_4)(HSO_4)^{2+}$.

first lowered by addition of sulphuric acid (to pH 1·15 and 0·98 respectively). It is evident that, as in the experiments with ferric chloride,[1] the sorption of both phosphate and iron occurs and that the sorption of each again passes through a maximum at a mole ratio of PO_4 : Fe of 1 : 1 or slightly greater. However, the amounts of phosphate and iron sorbed are not consistent with the sorption of $FeHPO_4^{+}$ ions together with Fe^{3+} ions.

It has been pointed out [4] that for the sorption of a complex ion of the type $FeH_xPO_4^{x+}$ together with that of Fe^{3+}, the following equation will apply

$$3N_{Fe} - N_{phosphate}(3 - x) = 1 \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where N_{Fe} and $N_{phosphate}$ represent the total number of moles of iron and phosphate sorbed respectively per equivalent of resin. This equation can be generalised for sorption of any one cationic complex together with free metal cations :

$$pN_{Fe} - qN_{phosphate} = 1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Now p is dependent on the charge on the free metal cations only (and is thus 3 for Fe^{3+}), but q depends on the charge on the complex ion and on the free ion, as can be seen from equation (1) [for which $q = (3 - x)$]. The value of q can be obtained by rearranging equation (2), and the values thus deduced are shown in Table 1. It can be seen that in every case $q > 2$, whilst from equations (1) and (2) it is apparent that for sorption of $FeHPO_4^{+}$ $x = 1$ and $q = 2$, and for sorption of $FeH_2PO_4^{2+}$ $x = 2$ and $q = 1$. Thus sorption of these ions, at least singly, is not indicated.

A possible explanation lies in the sorption of polynuclear complex ions. Thus for sorption of $Fe_2(PO_4)^{3+}$ ions together with Fe^{3+} ions, we have for *one equivalent* of resin

Moles of free Fe^{3+} sorbed = (total Fe) − (Fe in complex) = $N_{Fe} - 2N_{phosphate}$

Equivs. of free Fe^{3+} sorbed = $p(N_{Fe} - 2N_{phosphate})$

Equivs. of complex sorbed = $3N_{phosphate}$

Total equivs. sorbed = $1 = pN_{Fe} - (2p - 3)N_{phosphate}$, whence $q = 2p - 3$, or $q = 3$ (since $p = 3$). The use of the value of $p = 3$ appears to be justified here since in the absence of phosphate ($[PO_4]/[Fe] = 0$), 0·333 mole of Fe is sorbed per equivalent of resin.

In Table 1, certain complexes having values for q close to those found experimentally are indicated. Others are possible but the polynuclear complexes given are such that (*a*) it is possible to assign them structures containing phosphato-bridges $M{-}PO_4{-}M$ (or $M{-}HPO_4{-}M$) and (*b*) the complexes contain the lowest possible number of such bridges. The first of these conditions was decided on the basis of some studies of the magnetic properties of these systems [5] which have indicated that bridging occurs through phosphato-groups. The second condition appears reasonable when it is considered that a complex such as $M_3(PO_4)_2^{3+}$ (for example, for which $q = 3$, when $p = 3$) contains twice as many metal–oxygen bonds, which are subject to attack by a proton with consequent breakdown of the complex, as does $M_2(PO_4)^{3+}$, which ion is, therefore, likely to be the more stable in acid solution.

In the final column of Table 1 are given the values of $pN_{Fe} - qN_{phosphate}$, which from equation (2) should be unity, as is observed ($\pm 0{\cdot}03$) in all but two instances. This is satisfactory when account is taken of the fact that, where two complexes are indicated as having q values close to the experimental one, the average of these values has been used in the calculations; this involves the arbitrary assumption that the phosphate sorbed is divided equally between the two complexes.

The effect of lowering the initial pH of the ferric sulphate solution from 1·86 to 1·46 (Table 1) leads to a more marked sorption of $FeHPO_4^+$ ions (q approaches more closely to 2), although polynuclear ions are still sorbed as well. The stability of the $FeHPO_4^+$ ion is likely to be greater in solutions of lower pH, for whilst, if the HPO_4 group is bidentate, it contains two metal–oxygen bonds, like $Fe_2(PO_4)^{3+}$, it differs from that complex in that rupture of one metal–oxygen bond does not break down the complex, but yields instead $FeH_2PO_4^{2+}$ which can subsequently lose a proton to re-form $FeHPO_4^+$.

To lower the pH of the ferric sulphate solution still further (to 0·98, Table 1) required addition of an appreciable quantity of sulphuric acid, in accord with the inference already drawn that $FeSO_4^+$ ions exert a buffering effect. The formation of complete sulphato-ferric ions is apparent from the fact that in the absence of phosphate the resin is not saturated (less than 0·333 mole of Fe^{3+} sorbed per equiv.), in contrast to the experiments with ferric chloride solutions at the same pH (Table 2). It is difficult therefore to base many conclusions on the q values derived for this series, but the fact that they are higher than those for the two preceding experiments indicates that polynuclear, rather than $FeHPO_4^+$, ions are sorbed. Although the values of q might seem to indicate the sorption of $Fe_2(PO_4)(OH)^{2+}$ ($q = 4$), this seems unlikely at the pH (*ca.* 0·80) and sulphate concentrations concerned {cf. the solutions of higher pH [Table 1 (1) (2)] where there is no evidence for sorption of $Fe_2(PO_4)(OH)^{2+}$}. It is suggested that instead the ion $Fe_2(PO_4)(HSO_4)^{2+}$ is sorbed, but is converted into $Fe_2(PO_4)(OH)^{2+}$ during the washing of the resin—no sulphate was found in the eluate.

In the corresponding experiments with ferric chloride solutions (0·1M) (Table 2) evidence is again found for the sorption of polynuclear complexes. The values of q are the highest for the ferric chloride solution of highest pH and correspond to the sorption of $Fe_2(PO_4)(OH)_2^+$ or $Fe_2(PO_4)(OH)^{2+}$ ions. With the solution of pH 1·46 (cf. the ferric

[5] Holroyd, Jameson, Odell, and Salmon, Part V, in the press.

sulphate solution of pH 1·34) the $Fe_2(PO_4)^{3+}$ ions are sorbed in the main, whilst at the lowest pH values, which correspond to those used in the experiments reported in Part II,[1] the sorption of $FeHPO_4^+$ is indicated. The conditions in which the various ions are sorbed are consistent with the pH values at which they might be expected to be stable, and no complications arising from the formation of chloro-complexes are apparent. The values of $pN_{Fe} - qN_{phosphate}$ are close to unity (±0·03) in most cases.

TABLE 2. *Sorption of iron and phosphate by Zeo-Karb* 225 (H-*form*, 0·500 g.) *from solutions* (50 *ml.*) *containing ferric chloride and phosphoric acid.*

Solution		Resin						
$\frac{[PO_4]}{[Fe]}$	pH *	N_{Fe}	$N_{phosphate}$	q †	Possible complexes ‡	q for complexes	q (average)	$pN_{Fe} - qN_{phosphate}$
(1) Ferric chloride solution, pH 1·86; $p = 2·75$.								
0·06	1·40	0·365	—	—	—	—	—	1·00
0·33	1·02	0·442	0·047	4·60	*c*	4·50	4·50	1·00
0·48	0·95	0·450	0·056	4·25	*c*	4·50	4·50	0·99
0·74	0·90	0·480	0·058	5·52	*c*	4·50	4·50	1·06
0·94	0·90	0·504	0·138	2·80	*b* or *a*	3·50; 2·50	3·00	0·97
1·27	0·90	0·509	0·150	2·67	*a*	2·50	2·50	1·03
(2) Ferric chloride solution, pH 1·46; $p = 2·82$.								
0·00	1·20	0·355	—	—	—	—	—	1·00
0·33	0·92	0·530	0·165	3·00	*b* or *a*	3·64; 2·64	3·14	0·98
0·49	0·86	0·549	0·185	2·96	*b* or *a*	3·64; 2·64	3·14	0·97
0·75	0·84	0·585	0·238	2·73	*a*	2·64	2·64	1·02
0·94	0·84	0·598	0·252	2·72	*a*	2·64	2·64	1·02
1·28	0·84	0·604	0·317	2·22	*a* or *d*	2·64; 1·82	2·23	1·00
(3) Ferric chloride solution, pH 1·24; $p = 2·93$.								
0·00	0·99	0·341	—	—	—	—	—	1·00
0·19	0·88	0·499	0·165	2·80	*a*	2·86	2·86	0·99
0·41	0·78	0·509	0·213	2·31	*a* or *d*	2·86; 1·93	2·40	0·98
0·65	0·76	0·525	0·270	1·99	*d*	1·93	1·93	1·02
0·94	0·74	0·540	0·306	1·90	*d*	1·93	1·93	0·99
1·27	0·77	0·544	0·334	1·78	*d*	1·93	1·93	0·95
1·70	0·79	0·523	0·306	1·74	*d*	1·93	1·93	0·94

* † ‡ See Table 1.

In connection with these experiments with the ferric chloride solution, it will be seen from Table 2 that the value of p used is always less than 3, although it approaches that value as the pH of the solution is lowered. This arises from the fact that in the absence of phosphate the amount of iron sorbed is always greater than 0·333 mole per equiv., indicating that the " free " iron is sorbed as a mixture of Fe^{3+} together with one or more of its hydrolysis products [such as, *e.g.*, $Fe(OH)^{2+}$, for which $p = 2$]. The value of p used in each series of experiments has been determined from the value of $1/N_{Fe}$ obtained in the absence of phosphate. The trend towards $p = 3$ at the lower pH is to be expected from the accompanying repression of the hydrolyses.

The results of some anion-exchange studies of mixtures of ferric sulphate solutions (0·1M in Fe) with phosphoric acid solutions (0·3M) are given in Table 3. In this Table an attempt has been made, following a method previously described,[1,2] to account for the capacity of the resin samples by assuming (*a*) the sorption of $[Fe(PO_4)_3]^{6-}$ (see ref. 2), $[Fe(SO_4)_2]^-$, and SO_4^{2-} ions and (*b*) the sorption of $[Fe(PO_4)(SO_4)]^{2-}$ and SO_4^{2-} ions. The choice of the second assumption was prompted by the observation that the iron and phosphate were sorbed in approximately equimolecular amounts, as required by this assumption. It has already been noted [1] that a similar sorption of iron and phosphate in equimolecular amounts occurs with ferric chloride–phosphoric acid solutions, but only in the presence of a marked excess of chloride.

TABLE 3. *Sorption of iron, phosphate, and sulphate by I.R.A. 400 (phosphate form, 1·000 g.) from solutions (50 ml.) containing ferric sulphate and phosphoric acid.*

Solution		Resin				
					Capacity accounted for (%) †	
$\frac{[PO_4]}{[Fe]}$	pH *	N_{Fe}	$N_{phosphate}$	N_{SO_4}	(*a*)	(*b*)
0·78	1·14	$0·07_7$	$0·05_9$	$0·49_0$	93	98
1·38	1·14	$0·08_0$	$0·06_4$	$0·46_6$	88	93
2·21	1·20	$0·08_7$	$0·08_8$	$0·48_1$	96	96
3·41	1·24	$0·09_2$	$0·10_7$	$0·46_3$	97	93
5·34	1·28	$0·10_3$	$0·12_1$	$0·46_8$	98	93

* Of solution in equilibrium with the resin.

† By assuming (*a*) that all the phosphate is sorbed as $[Fe(PO_4)_2]^{6-}$, that the remaining iron present is sorbed as $[Fe(SO_4)_2]^-$ and the remaining sulphate is sorbed as SO_4^{2-}; (*b*) that within experimental error the iron and phosphate are present in equimolecular amounts ($N_{Fe} = N_{phosphate}$) in the $[Fe(PO_4)(SO_4)]^{2-}$ ion, with excess of sulphate present as SO_4^{2-}. For purposes of calculation it did not matter whether the value of N_{Fe} or $N_{phosphate}$ was taken as "correctly" representing both of them.

It can be seen from Table 3 that whilst the assumption of the sorption of $[Fe(PO_4)_2]^{6-}$, $[Fe(SO_4)_2]^-$, and SO_4^{2-} ions accounts more satisfactorily for the resin capacity at the higher ratio of $[PO_4]/[Fe]$ in solution, at the lower phosphate ion concentrations the sorption of the mixed complex ion $[Fe(PO_4)(SO_4)]^{2-}$ is indicated. This observation together with that made in the corresponding cation exchange experiments suggests that mixed sulphato-phosphato-ferric complexes may be formed more readily than mixed chloro-phosphato-ferric complexes.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, September 17th*, 1956.]

186. *Tracer Studies in Ester Hydrolysis. Part IV.* The Hydrolysis of Diphenylmethyl Formate and Acetate.*

By C. A. BUNTON, J. N. E. DAY, R. H. FLOWERS, P. SHEEL, and J. L. WOOD.

In hydrolysis of diphenylmethyl formate under acidic and basic conditions the acyl–oxygen bond is broken, but in an initially neutral solution alkyl–oxygen fission occurs. The latter result is supported by the observation of carbonium-ion capture by the thiocyanate ion in initially neutral solution. Acyl–oxygen bond fission is found for the acid hydrolysis of diphenylmethyl acetate.

MECHANISTIC studies of hydrolysis of carboxylic esters show that substitution by electron-releasing groups on the α-alkyl-carbon atom increases the ease of fission of the alkyl–oxygen bond.[1] In particular there is a parallelism between the S_N1 reactivity of an alkyl halide and the ease of alkyl–oxygen bond fission in the corresponding carboxylic ester. For example, Kenyon and his co-workers provided numerous instances of alkyl–oxygen bond fission in reactions of the hydrogen phthalates of secondary alcohols containing electron-releasing groups,[2] and this bond fission is found in the acid hydrolyses of *tert.*-butyl[3] and ethyldimethylpentyl acetates,[4] and in the acid, neutral, and basic hydrolyses of triphenylmethyl acetate.[5] It might be expected therefore that esters of diphenylmethanol would provide suitable systems for the observation of hydrolyses with alkyl–oxygen bond fission. Hydrolysis of the formate was examined under a variety of

* Part III, *J.*, 1956, 1079.

[1] Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686.
[2] Davies and Kenyon, *Quart. Rev.*, 1955, **9**, 203.
[3] Bunton and Wood, *J.*, 1955, 1522.
[4] Bunton, Hughes, Ingold, and Meigh, *Nature*, 1950, **161**, 680.
[5] Bunton and Konasiewicz, *J.*, 1955, 1354.

conditions (the results of the rate studies are tabulated). In accordance with observations on other alkyl formates [6] the attack of hydroxide ion (with acyl–oxygen bond fission) was very rapid. The acid hydrolysis is considerably slower than the alkaline hydrolysis, and it too involves acyl–oxygen bond fission. Rate comparisons with acid-catalysed hydrolyses of other non-sterically hindered esters [7] suggest a bimolecular rather than a

TABLE 1. *Rates of hydrolysis in aqueous dioxan.*

Solvent: aqueous 70% dioxan (except where otherwise specified).

(*A*) Diphenylmethyl formate at 35° (except where otherwise specified).

[HCl] (M)	0·0246	0·0491	0·0986	0·0986	0·0536	0·111
10^6k_1 (sec.$^{-1}$)	10·6, 10·3	20·3, 20·6	42·9, 44·3	1·45,* 1·54 *	73·2 †	169 †

k_A (at 0°) = 1·52 × 10^{-5}; k_A (at 35°) = 45·5 × 10^{-5} sec.$^{-1}$ mole^{-1} l.

* Temp. 0°. † Solvent: aq. 75% dioxan; temp. 50°.

(*B*) Effect of added reagents; [HCl] = 0·0986M.

Reagent	$H{\cdot}CO_2H$	NaCNS	$NaClO_4$		
[Reagent] (M)	0·115	0·0367	0·021	0·126	0·171
10^6k_1 (sec.$^{-1}$)	45·5	43·1	44·8	50·9	56·3

(*C*) Base hydrolysis; [$Ba(OH)_2$] = 0·005M; [Ester] = 0·008M.

Temp. 0°. k_2 = 0·430, 0·425 sec.$^{-1}$ mole^{-1} l. (independent expts.).

(*D*) Initially neutral hydrolysis; temp. 99·2°; initial k_1 = 6·10 × 10^{-6} sec.$^{-1}$.

Diphenylmethyl acetate. Temp. 99·5°.

[HCl] (M)	0·020	0·030	0·040	0·060
10^4k_1 (sec.$^{-1}$)	1·79	2·40	3·40	5·07

k_A = 8·3 × 10^{-4} sec.$^{-1}$ mole^{-1} l.

unimolecular mechanism. The rate dependence on temperature follows the equation: $k_A = 1{\cdot}41 \times 10^{-8} \exp(-16{,}100/RT)$. These values for the Arrhenius parameters are similar to those observed in other hydrolyses by mechanism $A_{Ac}2$ (see, *e.g.*, ref. 8). Similarly the ratio of the second-order rate coefficients for the acid and the basic hydrolysis is of the same order of magnitude as observed in bimolecular ester hydrolyses with acyl–oxygen bond fission.[7]

Hydrolysis of diphenylmethyl acetate was followed under acid conditions only. It was slower than that of the formate, and by extrapolation of the formate rate values to the temperature of the acetate runs we calculate that the formate is hydrolysed in acid *ca.* 55 times faster than the acetate. Determination of the position of bond fission in the acid hydrolysis of the acetate, by using ^{18}O as tracer, was complicated by the acid-catalysed oxygen exchange between water and diphenylmethanol. Since acetic acid undergoes exchange so rapidly under the experimental conditions it was pointless to study its abundance. The isotopic abundances of the diphenylmethanol isolated from control tests and from the acid hydrolyses are, however, consistent with hydrolysis by acyl–oxygen bond fission. Both esters therefore react by the same mechanism in acid solution.

Hydrolysis of the formate in initially neutral solution was much slower than in the presence of acid or alkali. The formic acid produced catalysed the hydrolysis, and the first-order rate coefficient quoted in Table 1 is therefore calculated from the initial rate. Tracer studies with diphenylmethanol isolated from hydrolysis in initially neutral solution showed that its oxygen was in part derived from the solvent, and control tests proved that exchange between alcohol and solvent could not account for this isotopic enrichment. There was therefore at least some alkyl–oxygen fission in the neutral hydrolysis. The exact amount could not be determined readily, partly because of the exchange already

[6] Humphreys and Hammett, *J. Amer. Chem. Soc.*, 1956, **78**, 521.
[7] Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1939, pp. 212—213.
[8] Drushel, *Annalen*, 1915, **39**, 113; **40**, 643; Skrabal and *et al.*, *Monatsh.*, 1926, **47**, 17, and later papers.

mentioned, but also because those ester molecules whose hydrolysis is catalysed by formic acid will undergo acyl–oxygen fission, and their number will increase as the reaction proceeds.

TABLE 2. *Position of bond fission.*

(1) *Diphenylmethyl formate.*

(i) Solvent: aqueous 70% dioxan. Temp. 35·0°. Isotopic abundance of water = 0·550 atom % excess. (Method A.)

	[HCl] (M)	Abundance of product (atom % excess)	Oxygen (%) derived from water
Hydrolysis:	0·0784	0·034	6
	0·141	0·042	7
Control:	0·0996	0·040	8

(ii) Solvent: aqueous 75% dioxan. Temp. 50°. Isotope measurements determined by density, relative to London tap water.

[HCl] (M)	Density of water (p.p.m.)	Density of water from product (p.p.m.)	Oxygen (%) derived from water
0·203	+293	+13, +4	4·4, 1·3
0·200	+298	+5	1·7

Control tests under the experimental conditions gave samples of diphenylmethanol which gave water of relative densities +20, +7 p.p.m.

(iii) Basic hydrolysis. Solvent: aqueous 70% dioxan. [NaOH] = 0·1M. Temp. 0°. Isotopic abundance of water = 0·727 atom % excess. Abundance of product = 0·008 atom % excess. (Method B.)

(iv) Initially neutral. Solvent: aqueous 70% dioxan. Temp. 99·5°. [Ester] = *ca.* M/7. Isotopic abundance of water = 0·476 atom % excess. (Method B.)

	Time (hr.)	Abundance of product (atom % excess)	Oxygen (%) derived from water
Hydrolysis:	54	0·270	57
	32	0·233	49
Control:	42[a]	0·140	29
	30[b]	0·042	8·8

$H{\cdot}CO_2H$: (*a*) 0·2M, (*b*) 0·1M.

(2) *Diphenylmethyl acetate.*

Solvent: aqueous 70% dioxan. Temp. 99·5°. Isotopic abundance of water = 0·483 atom % excess. (Method B.)

	[HCl] (M)	Time (hr.)	Abundance of product (atom % excess)	Oxygen (%) from water
Hydrolysis:	0·06	3	0·294	61
	0·12	1·5	0·366	76
Control:	0·06	1·7	0·283	59
	0·12	0·8	0·390	81

In confirmation of these postulated mechanisms, we find that the thiocyanate ion intervenes in the neutral, but not in the acid, hydrolysis. This reagent forms a stable product with the diphenylmethyl cation, and so a method is available for the detection of this ion. In the hydrolysis of diphenylmethyl chloride in aqueous 70% dioxan, at 35°, almost half the carbonium ions produced are captured by the thiocyanate ion. Under initially neutral conditions, in the same solvent at 99·5°, *ca.* 20% of the total reaction is diverted to alkyl thiocyanate or *iso*thiocyanate.

EXPERIMENTAL

Materials.—Diphenylmethyl formate was first prepared by Bacon[9] by interaction of diphenylmethyl chloride and sodium formate in formic acid. This method was used for some samples; it was necessary to use carefully dried materials. After 3 days' heating on a steam-bath the product was extracted with light petroleum, volatile materials were pumped off, and after distillation (b. p. 104°/0·4 mm.) the ester slowly crystallised, having m. p. 22° (Found: C, 79·0; H, 5·9. Calc. for $C_{14}H_{12}O_2$: C, 79·2; H, 5·7%).

Later samples of the ester were prepared more simply by reaction of diphenylmethanol with acetic formic anhydride containing a trace of sodium formate. Acetic acid and excess of

[9] Bacon, *Amer. Chem. J.*, 1905, **33**, 88.

anhydride were pumped off. The ester crystallised. A third method was used with partial success : diphenylmethanol was heated with sodium formate in dry formic acid saturated with hydrogen bromide; ester prepared by this method did not solidify and probably contained diphenylmethanol and possibly bisdiphenylmethyl ether.

Diphenylmethyl acetate was prepared by heating acetic anhydride containing diphenylmethanol under reflux for 3 hr. The solvent was pumped off; the ester purified by crystallisation from light petroleum had m. p. 41°.

Kinetic Runs.—Reactions were carried out in aqueous dioxan which, in general, contained 70% by volume of purified dioxan. The kinetics were followed by acid–base titration; in experiments on the formate it was essential to avoid building up of local concentrations of alkali during titration, because of the high rate of basic hydrolysis.

Both thiocyanate ion and picric acid were tried as intervening agents. Tests on the hydrolysis of diphenylmethyl chloride at 35°, in aqueous 70% dioxan containing hydrochloric acid, showed that 44% of the total reaction product was alkyl thiocyanate or *iso*thiocyanate. Thiocyanate ion did not intervene in the acid hydrolysis, and its small effect on the rate (Table 1) was due to its ionic strength effect; this ion did, however, intervene effectively in the neutral hydrolysis of diphenylmethyl formate at 99°. Picric acid did not intervene in the hydrolysis of diphenylmethyl chloride under the conditions of the acid hydrolysis of diphenylmethyl formate; its use was not investigated further.

Position of Bond Fission.—Tracer experiments were made with the solvent water enriched in ^{18}O. In the early work the isotopic abundance was determined by density measurements; mass-spectrometric assay was used for later samples.

Diphenylmethanol, isolated from hydrolysis under kinetically controlled conditions, was purified by recrystallisation from light petroleum and dried in a vacuum-desiccator. The isotopic abundances of the isolated samples were determined by various methods. (i) *Ca.* 4 g. were cracked over platinised quartz at 1100° in a stream of dried, oxygen-free hydrogen, and the oxides of carbon so formed were then reduced to water over thoriated nickel. The general conditions were those described by Russell and Fulton.[10] The isotopic abundance of this water was determined by density measurements, by procedures already described,[11] or after electrolysis of a small part in a divided cell, by mass-spectrometric assay (method A). (ii) The alcohol was pyrolysed to carbon monoxide *in vacuo* in a carbon tube heated in an R.F. induction furnace. The carbon monoxide was analysed mass spectrometrically (method B). To minimise errors due to dilution and isotopic fractionation similar methods of analysis were used for the water and the diphenylmethanol.

Discussion

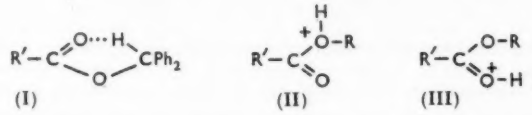
Hydrolysis of diphenylmethyl formate in alkaline solution by mechanism $B_{Ac}2$ is very rapid, as might be expected from consideration of the known properties of formate esters.[6] This high reactivity is not found in acid hydrolysis, and similarly diphenylmethyl acetate is less reactive than its aliphatic counterpart.[12] This comparatively low reactivity in acid solution is therefore common to both formate and acetate. The facility of the alkaline hydrolysis, together with inspection of molecular models, suggests that steric hindrance at the acyl(carbonyl)-carbon atom is of minor importance, and tracer studies show that in both alkaline and acid solution the reagent attacks this atom. The results in acid solutions were somewhat unexpected because alkyl–oxygen bond fission is observed in the acid hydrolyses of the acetates of triphenylmethanol [5] and tertiary aliphatic alcohols,[3,4] compounds which give respectively more and less stable carbonium ions than are derived from a diphenylmethyl compound.

This comparatively low reactivity in acid solution of both the formate and acetate of diphenylmethanol is probably due to the lowering of the basicity of these esters by substitution of two phenyl groups on the alkyl-carbon atom.

Hydrogen bonding,[13] as in (I), would reduce the basicity of the ester molecule and

[10] Russell and Fulton, *Ind. Eng. Chem., Anal.*, 1933, **5**, 384.
[11] Datta, Day, and Ingold, *J.*, 1939, 838.
[12] Bell, Dowding, and Noble, *J.*, 1955, 3106.
[13] Curran, *J. Amer. Chem. Soc.*, 1945, **67**, 1835.

might also facilitate acyl–oxygen bond fission in the neutral and basic hydrolyses. The $-I$ effect of the phenyl groups, while reducing the basicity of the ester, would facilitate this hydrogen bonding. These effects will reduce the standing concentration of the



(I) (II) (III)

conjugate acid of the ester and hence the overall rate of reaction. This factor alone does not explain the apparently anomalous position of bond fission in the acid hydrolysis. Protonation of a carboxylic ester may occur on either the ethereal or the carbonyl-oxygen atom, giving conjugate acid (II) and (III). The relative amounts of these acids will depend on the relative basicities of the two oxygen atoms, and either of them may in principle be the reactive species in any acid hydrolysis. There is considerable evidence that acid-catalysed alkyl–oxygen bond fission gives a carbonium ion, by a reaction which should occur more readily in structure (II), where the positive charge is largely on the atom adjacent to the breaking bond. Acid hydrolysis with acyl–oxygen bond fission requires addition of a water molecule to the acyl(carbonyl)-carbon atom,[14] except in certain special systems where a unimolecular mechanism can be observed.[1,15] This addition should be facilitated by protonation of the acyl-oxygen atom, as in structure (III). We might therefore expect the relative ease of acyl– or alkyl–oxygen bond fission to be governed, not only by the tendency of the alkyl group to form a carbonium ion, but also by the position of protonation. Substitution of two phenyl groups on the α-alkyl-carbon atom will reduce the basicity of both the oxygen atoms in an ester molecule, hence tending to reduce the rate of acid hydroysis, but the effect will be greater on the nearer, ethereal oxygen atom. Structure (III) will therefore be favoured over structure (II), and hence attack of water molecules on the acyl-carbon atom, with consequent acyl–oxygen bond fission, will be preferred, despite the high stability of the diphenylmethyl carbonium ion.[16]

These considerations do not apply to hydrolysis in neutral solution (though our experimental observations are complicated by autocatalysis by formic acid). Here the mechanism should be governed solely by the relative ease of heterolysis of the alkyl–oxygen bond, and of bimolecular attack on the acyl-carbon atom. Tracer experiments prove the existence of some alkyl–oxygen bond fission, although the complications of autocatalysis of both hydrolysis and subsequent oxygen exchange between the alcohol and water prevent our determining its exact extent. Further, in initially neutral solution, diphenylmethyl formate is hydrolysed more rapidly than are *tert.*-butyl carboxylates,[17] but less rapidly than is triphenylmethyl acetate.[5] This rate sequence for neutral hydrolysis is that predicted from the relative ease of formation of the carbonium ions. The intervention of thiocyanate ion in neutral, but not in acid, hydrolysis supports the mechanisms which we propose.

The authors are indebted to Professors E. D. Hughes, F.R.S., and C. K. Ingold, F.R.S., for their valuable suggestions, and to Professor E. Watson and Dr. D. R. Llewellyn for a generous supply of isotopically enriched water.

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[14] Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1626.
[15] Long and Purchase, *ibid.*, 1950, **72**, 3267.
[16] Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603.
[17] Bunton, Comyns, Graham, and Quayle, *J.*, 1955, 3817.

187. 1 : 2-5 : 6-*Di*-O-iso*propylidene*-α-D-*glucofuranose* 3-(*Methyl Sulphate*).

By A. B. Foster and E. B. Hancock.

1 : 2-5 : 6-Di-*O-iso*propylidene-α-D-glucofuranose 3-(methyl sulphate) is obtained by oxidation of the corresponding methyl sulphite ester, and is converted into the 3-(sodium sulphate) by sodium iodide in acetone. The value of this new synthetical route is limited by the acid lability of the 3-(methyl sulphate).

Methods developed [1] for the preparation of carbohydrate sulphates involve the direct introduction of the sulphate residue. Subsequent reactions are frequently rendered difficult by the inconvenient properties conferred by the $RO{\cdot}SO_2{\cdot}O$ grouping. Thus, there is a need for methods which employ protected sulphate groups so that the salt of the free sugar sulphate ($RO{\cdot}SO_2{\cdot}O^-Y^+$) can be formed as the final stage of synthesis. From this viewpoint we have examined the reaction sequence

$$ROH \xrightarrow{A} \underset{(I)}{RO{\cdot}SO{\cdot}OMe} \xrightarrow{B} \underset{(II)}{RO{\cdot}\overset{\overset{a}{\downarrow}}{SO_2}{\cdot}\overset{\overset{b}{\downarrow}}{O}Me} \xrightarrow{C} RO{\cdot}SO_2{\cdot}O^-X^+$$

Stage *A* and some reactions of methyl sulphite esters (I) have been described elsewhere,[2] stages *B* and *C* and some properties of the hitherto unknown carbohydrate derivatives (II) are now outlined.

Oxidation of methyl sulphite esters (I) to methyl sulphate esters (II) may be accomplished, in moderate yield, by the use of calcium permanganate in aqueous acetic acid.[3] Crystalline 1 : 2-5 : 6-di-*O-iso*propylidene-α-D-glucofuranose 3-(methyl sulphate) was obtained thus but oxidation of (−)-menthyl methyl sulphite and 1 : 2-3 : 4-di-*O-iso*propylidene-α-D-galactopyranose 6-(methyl sulphite) gave only oily products. Dimethyl sulphite and di*iso*propyl sulphite were readily oxidized to the corresponding dialkyl sulphates. Active manganese dioxide [4] had no effect on dimethyl sulphite. All these dialkyl sulphates decompose on storage: the only stable dialkyl sulphates so far encountered are the cyclic sulphates of *cis*- and *trans-cyclo*hexane-1 : 2-diol.[5]

1 : 2-5 : 6-Di-*O-iso*propylidene-α-D-glucofuranose 3-(methyl sulphate) and sodium iodide in acetone yield the corresponding 3-(sodium sulphate) although the solubility of the salt in acetone complicates the isolation procedure. Cholesteryl 3-(methyl sulphate) is reported [6] to yield the 3-(sodium sulphate) by reaction with sodium iodide in acetone although no experimental details were provided. In this case the 3-(methyl sulphate) was prepared by the action of diazomethane on cholesteryl 3-(pyridinium sulphate). (−)-Menthyl methyl sulphate and dimethyl sulphate react readily with sodium iodide in acetone to yield sodium (−)-menthyl sulphate and sodium methyl sulphate, respectively; di*iso*propyl sulphate reacts less readily to give sodium *iso*propyl sulphate.

Hydrolysis by acid, or by alkali followed by acid, of 1 : 2-5 : 6-di-*O-iso*propylidene-α-D-glucofuranose 3-(methyl sulphate) gave mainly D-glucose together with traces of unidentified substances. Similar products were obtained when 1 : 2-5 : 6-di-*O-cyclo*hexylidene-α-D-glucofuranose 3-(barium sulphate) [7] was treated similarly. D-Allose, which would be expected to be formed if Walden inversion occurred at $C_{(3)}$ during hydrolysis of the D-glucose sulphate derivatives, could not be detected in the reaction mixtures. Walden

[1] Percival, *Quart. Rev.*, 1949, **3**, 369.
[2] Foster, Hancock, Overend, and Robb, *J.*, 1956, 2589.
[3] Garner and Lucas, *J. Amer. Chem. Soc.*, 1950, **72**, 5497.
[4] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.
[5] Foster, Hancock, and Overend, *Chem. and Ind.*, 1956, 1144.
[6] McKenna and Norymberski, *ibid.*, 1954, 961.
[7] Bera and Foster, unpublished results.

inversion does occur in simpler compounds: thus sodium (+)-1-methylpropyl sulphate yields (−)-butan-2-ol on basic hydrolysis.[8]

Dissolution of 1 : 2-5 : 6-di-*O-iso*propylidene-α-D-glucofuranose 3-(methyl sulphate) in aqueous acetic acid at 40° revealed (by paper-chromatographic and paper-ionophoretic analysis [9]) that the methyl ester group was much more labile in acid than were the *O-iso*-propylidene residues and that in the main the following reaction sequence occurred: 1 : 2-5 : 6-di-*O-iso*propylidene-α-D-glucofuranose 3-(methyl sulphate) $\xrightarrow{\text{fast}}$ 1 : 2-5 : 6-di-*O-iso*propylidene-α-D-glucofuranose 3-(sulphate) ⟶ D-glucose 3-sulphate $\xrightarrow{\text{slow}}$ D-glucose. The alternative initial reacton (*i.e.* cleavage at *a* in II) is negligible. The lability of the methyl ester group in acid media largely deprives the reaction sequence *A* ⟶ *B* ⟶ *C* of value as a method for carbohydrate sulphate synthesis and in view of this, alternative methods for synthesizing compounds of type (II) were not investigated.

Experimental

1 : 2-5 : 6-*Di*-O-iso*propylidene*-α-D-*glucofuranose* 3-(*Methyl Sulphate*).—To a solution of 1 : 2-5 : 6-di-*O-iso*propylidene-D-glucofuranose 3-(methyl sulphite) [2] (10 g.) in glacial acetic acid (20 ml.) cooled to 0° was added a solution of calcium permanganate (7·4 g.) in water (10 ml.) so that the temperature was kept below 15°. Reaction was complete when a permanent colour was produced. Thereafter the mixture was poured slowly into a cold solution of sodium carbonate (25 g.) in water (50 ml.), excess of permanganate was decomposed with sodium dithionite, and the mixture was extracted with ether (6 × 50 ml.). Evaporation of the dried ($MgSO_4$) extracts and crystallization from ether gave the *product* (4·5 g., 43%), m. p. 120—126° (decomp.), $[\alpha]_D^{22}$ −84·0° (*c*, 0·762 in $CHCl_3$) (Found: C, 43·6; H, 6·6; S, 9·15. $C_{13}H_{22}O_9S$ requires C, 44·1; H, 6·2; S, 9·0%). After 2 weeks at room temperature extensive decomposition had occurred. By a similar procedure dimethyl sulphate (24%) and di*iso*propyl sulphate (42%) were obtained from the corresponding sulphites. Application to 1 : 2-3 : 4-di-*O-iso*propylidene-α-D-galactopyranose 6-(methyl sulphite) [2] and (−)-menthyl methyl sulphite [2] gave oils which decomposed on attempted distillation or on storage at room temperature.

Action of Sodium Iodide in Acetone on 1 : 2-5 : 6-*Di*-O-iso*propylidene*-α-D-*glucofuranose* 3-(*Methyl Sulphate*).—A solution of sodium iodide (0·34 g.) in acetone (5 ml.) was added to one of 1 : 2-5 : 6-di-*O-iso*propylidene-α-D-glucofuranose 3-(methyl sulphate) (0·4 g.) in acetone (10 ml.), and the mixture stored at room temperature overnight. The solution was evaporated, the residue dissolved in water, and the aqueous solution extracted with ether and then diluted to 50 ml. Iodide ion was removed by addition of the exact amount (determined by titration) of aqueous silver nitrate, and the remaining solution freeze-dried. The residue was extracted with boiling acetone and the extract concentrated to give 1 : 2-5 : 6-*di*-O-iso*propylidene*-α-D-*glucofuranose* 3-(*sodium sulphate*) (0·29 g., 71%), m. p. 135—136° (decomp.), $[\alpha]_D^{19}$ 0° (in water) (Found: S, 8·3. $C_{12}H_{19}O_9SNa$ requires S, 8·8%).

Dimethyl sulphate, di*iso*propyl sulphate, and (−)-menthyl methyl sulphate reacted rapidly with sodium iodide in acetone and after 1 min. at room temperature sodium methyl sulphate, (93%), sodium *iso*propyl sulphate (42%) and *sodium* (−)-*menthyl sulphate* {42%; m. p. 146° (decomp.), $[\alpha]_D^{17\cdot5}$ −61·8° (*c*, 1·0 in water) (Found: S, 11·6. $C_{10}H_{19}O_4SNa$ requires S, 12·4%)} had separated. The last is appreciably soluble in acetone.

Hydrolysis of 1 : 2-5 : 6-*Di*-O-iso*propylidene*-α-D-*glucofuranose* 3-(*Methyl Sulphate*).—(a) A solution of the methyl sulphate ester (0·123 g.) in N-sulphuric acid (5 ml.) was boiled under reflux for 1·5 hr. and then neutralized with barium hydroxide. Paper ionophoresis [9] of the solution in borate buffer (pH 10) for 2·5 hr. at 900 v showed the presence of D-glucose and traces of other, unidentified reducing substances (aniline hydrogen phthalate [10]): D-allose was absent from the hydrolysate. A mixture of apparently similar composition was obtained by the acidic hydrolysis of 1 : 2-5 : 6-di-*O-cyclo*hexylidene-α-D-glucofuranose 3-(barium sulphate) [6] {m. p. 220—260° (charring), $[\alpha]_D^{19}$ *ca.* 0° (*c*, 1·28 in water)}.

(b) A solution of the ester sulphate (0·120 g.) in 2N-sodium hydroxide (5 ml.) was boiled

[8] Burwell and Holmquist, *J. Amer. Chem. Soc.*, 1948, **70**, 878.
[9] Foster, *Chem. and Ind.*, 1952, 1050; *J.*, 1953, 982.
[10] Partridge, *Nature*, 1949, **164**, 443.

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under reflux for 1·5 hr. (extensive liberation of sulphate ion) and then de-ionized [Amberlite IR-120(H^+)]. *iso*Propylidene residues were removed by acidic hydrolysis and the neutralized solution was examined by paper ionophoresis; a composition similar to that in (*a*) was observed. Identical results were obtained with 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-α-D-glucofuranose 3-(barium sulphate).

(c) A solution of the ester sulphate (0·275 g.) in acetic acid (12·5 ml.) and water (7·5 ml.) was maintained at 40° {$[\alpha]_D$ −0·34° ⟶ +0·12° (constant value) in 9 hr.}. From time to time the composition of the solution was examined (1) by paper chromatography: after irrigation with the organic phase of a butanol–ethanol–water (5 : 1 : 4) mixture and development with aniline hydrogen phthalate [10] (reducing sugars), *iso*propylidene derivatives could be detected by spraying with trichloroacetic acid (25% solution in 50% aqueous methanol), heating, and then spraying with aniline hydrogen phthalate; and (2) by paper ionophoresis, the previously described [9] apparatus and technique being used, with borate (pH 10) and glycine (pH 11) buffers and development as in (1). Suitable reference compounds were always included. It was apparent that in the main the reaction sequence was that outlined in the Discussion.

Acknowledgment is made to Professor M. Stacey, F.R.S., and Dr. W. G. Overend for their interest in this work. Thanks are due to Dr. N. K. Richtmyer for a sample of D-allose and Mr. B. C. Bera for a specimen of 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-α-D-glucofuranose 3-(barium sulphate). One of us (E. B. H.) thanks the D.S.I.R. for a grant.

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188. *Constitution of Dalbergin. Part II.*[1]

By V. K. AHLUWALIA and T. R. SESHADRI.

Dalbergin is shown by degradative and synthetic evidence to be a monomethyl ether of 4-phenylæsculetin, and is the first natural 4-phenylcoumarin. Its monomethyl ether is a minor component of the heartwood of *Dalbergia sissoo*.

EARLIER [1] it was shown that dalbergin $C_{15}H_8O_2$(OMe)(OH), the chief chemical component of the heartwood of *Dalbergia sissoo*, is neither a derivative of 3-phenylæsculetin (as proposed by Dutt and Kathpalia [2]) nor of 3-phenyldaphnetin. In the present study the infrared spectrum has been found to include prominent absorption at 3200 (phenolic OH), 1680 (C=O), 1610 (−C=C−), 1540, 1505, and 1450 cm.$^{-1}$ (aromatic double bonds). The frequencies of the C=O and the C=C group suggest that they are conjugated. The behaviour of dalbergin with alkali agrees with that of an αβ-unsaturated lactone. That the phenolic hydroxyl and the methoxy-group are *ortho* to each other is shown by the ferric chloride colour of nordalbergin, which moreover forms a methylenedioxy-derivative. The methyl ether of dalbergin is stable, even on long boiling, to 20% alcoholic potassium hydroxide. Dalbergin and its methyl ether give an unusual colour reaction with magnesium and alcoholic hydrochloric acid, pink changing to blue and red. These results led to a suspicion that dalbergin was probably not a coumarin derivative,[1] but *O*-methyldalbergin with dimethyl sulphate and methanolic alkali gives an *O*-methyl ether of the corresponding cinnamic acid. Oxidation of *O*-methyldalbergin (I) with cold neutral permanganate has yielded benzoic acid, oxalic acid, and 2-hydroxy-4 : 5-dimethoxybenzophenone (II). The consequence that *O*-methyldalbergin is 6 : 7-dimethoxy-4-phenylcoumarin has been confirmed by synthesis. Nordalbergin and *O*-methyldalbergin are identical, respectively, with 4-phenylæsculetin (from 1 : 2 : 4-triacetoxybenzene and ethyl benzoylacetate) and its dimethyl ether. On the other hand, these dalbergin

[1] Part I, Ahluwalia, Sawhney, and Seshadri, *J. Sci. Ind. Res., India*, 1956, **15**, *B*, 66.
[2] Dutt and Kathpalia, *Indian Soap J.*, 1953, **18**, 213.

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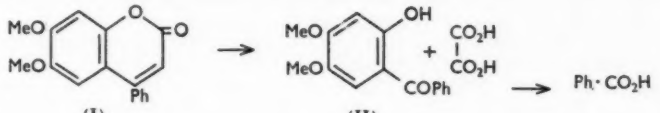
derivatives differ from 4-phenyldaphnetin [3] and its dimethyl ether. The position of the methoxyl group in dalbergin is under investigation.



(I) (II)

During the extraction of dalbergin we isolated *O*-methyldalbergin as a minor constituent, which suggests that stepwise methylation of nordalbergin takes place in the plant, possibly the more active hydroxyl group being first methylated to yield dalbergin.

Though coumarin derivatives (C_9 system) with various modifications have been found in Nature in large numbers, phenylcoumarins have not been known as natural products. Dalbergin and *O*-methyldalbergin represent naturally occurring simple members of the 4-phenylcoumarin group which are analogous to the structures found in brazilin and hæmatoxylin. Wedelolactone [4] is a 3-phenylcoumarin analogous to naturally occurring *iso*flavonoids which are fairly frequent. Dalbergin could also be considered as related to benzophenone derivatives occurring in Nature; possibly the latter are produced by the degradation of 4-phenylcoumarins. Similarly stilbenes could arise from 3-phenylcoumarins. These considerations would bring together the structural chemistry of naturally occurring flavonoids and *iso*flavonoids, 3- and 4-phenylcoumarins, benzophenones, and stilbenes.

Experimental

Extraction (*Dalbergin and* O-*Methyldalbergin*).—Shavings of the heartwood (2 kg.) were extracted with hot light petroleum (b. p. 60—80°; 3 × 6 hr.) to remove oils and then with boiling benzene (4 × 6 hr.). The benzene extract was concentrated to 300 c.c. and left for 2 days at 0°. Crystals (A) were deposited. The benzene solution was diluted with ether and the solution separated into alkali-soluble [mixed with the above solid (A)] and neutral components. The neutral product crystallised from methyl alcohol as colourless elongated rectangular prisms and rods (2·0 g.), m. p. 145—146° undepressed by *O*-methyldalbergin.[1] With magnesium and alcoholic hydrochloric acid it gave a feeble pink colour which changed to deep blue on addition of more magnesium; this was stable for some time and finally became deep red.

The solid (A) was passed in hot ethyl acetate (1 l.) through a column of alumina (8″) and eluted with hot ethyl acetate (2 l.). The coloured impurities were retained. The total eluate on concentration gave directly pure dalbergin (11·5 g.), m. p. 209—210°.

OO-*Methylenenordalbergin*.—Nordalbergin [1] was refluxed with an excess of methylene iodide and potassium carbonate in acetone for 8 hr. The *product* crystallised from methyl alcohol as thick tablets, m. p. 142—143° (Found: C, 72·2; H, 3·8. $C_{16}H_{10}O_4$ requires C, 72·2; H, 3·8%).

Permanganate Oxidation.—A solution of *O*-methyldalbergin (2 g.) in acetone (100 c.c.) was treated with potassium permanganate (10 g.) in small quantities and left for 24 hr. at room temperature (occasional shaking); acetone was distilled off, and the residue suspended in water (100 c.c.) and saturated with sulphur dioxide. The mixture was extracted with ether [aqueous mother-liquor (A)], and the extract washed with water. The ether extract was extracted with 5% aqueous sodium hydrogen carbonate (B), 10% aqueous sodium hydroxide (C), and then water, and the solvent distilled off (residue D). The carbonate extract (B), on acidification, ether-extraction [the remaining aqueous solution was mixed with the above aqueous mother-liquor (A)], and removal of the solvent, gave benzoic acid (0·7 g.), m. p. and mixed m. p. 120—121° (from water). The sodium hydroxide extract (C), worked up similarly, gave a small amount of oil. Its dinitrophenylhydrazone crystallised from acetic acid as deep red elongated rectangular plates, m. p. 254—256° alone or mixed with 2-hydroxy-4 : 5-dimethoxybenzophenone 2 : 4-dinitrophenylhydrazone (Found: C, 57·3; H, 4·5. $C_{21}H_{18}O_7N_4$ requires C, 57·5; H, 4·2%). The neutral residue (D) (0·1 g.) on crystallisation from methanol melted at 144—145° (unchanged methyldalbergin).

[3] Kostanecki and Weber, *Ber.*, 1893, **26**, 2906.
[4] Govindachari, Nagarajan, and Pai, *J.*, 1956, 629.

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The aqueous mother-liquor (A) was distilled under reduced pressure, and the residue dried and extracted with hot ethyl acetate (3 × 25 c.c.). After evaporation of the extract the residue of oxalic acid crystallised from ether–light petroleum as prisms (50 mg.), m. p. and mixed m. p. 100—101°.

Degradation of O-*Methyldalbergin to* 2 : 4 : 5-*Trimethoxy*-β-*phenylcinnamic Acid.*—*O*-Methyldalbergin (2 g.) was heated with dimethyl sulphate (22·5 c.c.), methyl alcohol (30 c.c.), and 10% aqueous potassium hydroxide (80 c.c.).[5] The *product* crystallised from methanol as pale yellow plates (1·0 g.), m. p. 170—171° (Found: C, 68·6; H, 5·7. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·8%).

7 : 8-*Dimethoxy*-4-*phenylcoumarin.*—7 : 8-Dihydroxy-4-phenylcoumarin[3] was methylated by use of dimethyl sulphate, potassium carbonate, and acetone. The *product* crystallised from alcohol as rectangular prisms, m. p. 135—136° (Found: C, 71·9; H, 5·3. $C_{17}H_{14}O_4$ requires C, 72·4; H, 5·0%).

6 : 7-*Dihydroxy*-4-*phenylcoumarin* (*Nordalbergin*).—This was prepared from hydroxyquinol triacetate[6] (55 g.), ethyl benzoylacetate[7] (42 g.), and 75% sulphuric acid (400 c.c.), under conditions similar to those adopted for 4-methylæsculetin,[8] the *product* being purified through the borate complex. It crystallised from alcohol as rectangular tablets and tiny prisms (30 g.), m. p. 267—268° undepressed by nordalbergin,[1] and gave a deep green colour with alcoholic ferric chloride and with magnesium and hydrochloric acid a pink colour which changed to blue and finally red (Found: C, 70·5; H, 3·7. $C_{15}H_{10}O_4$ requires C, 70·9; H, 3·9%).

The diacetate (acetic anhydride and pyridine) crystallised from alcohol as rectangular prisms and rods, m. p. and mixed m. p. 157—158°.

6 : 7-*Dimethoxy*-4-*phenylcoumarin* (*O-Methyldalbergin*).—6 : 7-Dihydroxy-4-phenylcoumarin was methylated by use of methyl sulphate, potassium carbonate, and acetone. The *product* crystallised from methyl alcohol as prisms and rods, m. p. and mixed m. p. 145—146° (Found: C, 72·9; H, 5·1. $C_{17}H_{14}O_4$ requires C, 72·4; H, 5·0%). With magnesium and hydrochloric acid it gave the same colour reaction as *O*-methyldalbergin. The trimethoxy-β-phenylcinnamic acid obtained as above melted at 170—171°, undepressed by a sample obtained from *O*-methyldalbergin.

We thank the Council of Scientific and Industrial Research, India, for a research grant and Sadtler and Son, Philadelphia, for the infrared spectrum.

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[5] Cf. Robertson, Waters, and Jones, *J.*, 1932, 1683.
[6] *Org. Synth.*, 1925, **4**, 35.
[7] *Ibid.*, 1943, **23**, 35.
[8] *Ibid.*, 1925, **4**, 45.

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189. *Bromination of Triterpenoids of the Oleanane and Ursane Series.*

By O. P. Arya and R. C. Cookson.

Esters of β-amyrin and of oleanolic acid are brominated first at $C_{(12)}$ and then at $C_{(18)}$, while 18α-β-amyrin and α-amyrin are brominated at $C_{(12)}$ only. Transformations of the bromides are described.

Esters of α- and β-amyrin can be brominated.[1-5] We find that α-amyrin acetate or benzoate (Ia) takes up only one mol. of bromine in acetic acid–carbon tetrachloride, whereas β-amyrin acetate or benzoate (Ib) takes up one mol. rapidly and a second more slowly. The resulting bromo-α-amyrin and its acetate agreed in m. p. with Vesterberg's compounds,[1,3] and the benzoate roughly corresponded with Zinke, Friedrich, and Rollett's ester.[2] Our monobromo-β-amyrin acetate also had the m. p. reported by Vesterberg,[1,4]

[1] Vesterberg, *Ber.*, 1890, **23**, 3186.
[2] Zinke, Friedrich, and Rollett, *Monatsh.*, 1920, **41**, 253.
[3] Zinke, *ibid.*, 1921, **42**, 439.
[4] Rollett, *ibid.*, 1922, **43**, 413.
[5] *Idem, ibid.*, 1926, **47**, 437.

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but the benzoate seems to be different from any of the monobromo-β-amyrin benzoates reported by Rollett [5] who may well have had mixtures.

Reduction of each monobromoamyrin with sodium and alcohol gave back the appropriate amyrin, proving that the bromination had not been attended with rearrangement of the carbon skeleton, and making it probable that the double bond in the bromides still occupied its original position. The great stability of the monobromides to base—for example, monobromo-α-amyrin was unchanged by long boiling with 10% potassium hydroxide in diethylene glycol (250°)—at once suggested that the bromine atom might be attached to a doubly bound carbon atom, probably $C_{(12)}$. This was verified by oxidation of monobromo-β-amyrin benzoate by chromic acid to an αβ-unsaturated ketone, with light absorption maxima at 1680 cm.$^{-1}$ and at 269 mμ. These are the spectral properties expected [6] of the bromo-ketone (IIIb), the ultraviolet maximum of the 12-en-11-one being shifted about 20 mμ to longer wavelengths by the 12-bromine atom. Reduction of monobromo-11-oxo-β-amyrin benzoate (IIIb) with lithium aluminium hydride, followed by acetylation, led to a bromo-diene, characterised as a 9(11) : 12-diene by its light absorption ($\lambda_{max.}$ 283 mμ) and high dextrorotation. Reduction of this diene with sodium and alcohol, and acetylation, indeed produced 3β-acetoxy-β-amyra-9(11) : 12-diene. Preparation of the bromo-ketone (IIIb) and bromo-diene (IVb) proves the absence of bromine at $C_{(9)}$ and $C_{(11)}$.

Monobromo-α-amyrin acetate and benzoate (IIa) were converted into the analogous compounds (IIIa) and (IVa) in the same way.

12-Bromo-α-amyrin benzoate did not react further with bromine in acetic acid, but 12-bromo-β-amyrin acetate or benzoate took up a second mol. of bromine in a few hours at room temperature, to form a mixture from which was isolated a dibromo-β-amyrin ester, the benzoate agreeing in m. p. with a dibromo-β-amyrin benzoate obtained by Zinke, Friedrich, and Rollett.[2]

Chromic acid in acetic acid oxidised dibromo-β-amyrin acetate or benzoate to the corresponding dibromo-11-ketone ($\lambda_{max.}$ 269 mμ), also produced by bromination of the appropriate ester of 12-bromo-11-oxo-β-amyrin (IIIb). The second atom of bromine can therefore be attached only to $C_{(9)}$ or $C_{(18)}$.

As a test of the latter possibility, the acetate of the dibromide was heated with collidine at 300°. Instead of the expected elimination, reduction occurred, yielding an isomer of 12-bromo-11-oxo-β-amyrin acetate. Similarly, collidine or zinc and acetic acid reduced dibromo-β-amyrin acetate to an isomer of 12-bromo-β-amyrin acetate, identified as 12-bromo-18α-β-amyrin acetate (V) when the identical substance was produced by brominating 18α-β-amyrin acetate. 12-Bromo-18α-β-amyrin acetate was oxidised to 12-bromo-11-oxo-18α-β-amyrin acetate identical with the monobromo-ketone formed on reduction of dibromo-11-oxo-β-amyrin acetate. Since normal 12-bromo-β-amyrin acetate and its 11-oxo-derivative were stable to collidine under conditions that reduced the dibromo-compounds to the 18α-isomers, the isomerisation is produced by reduction and the second atom of bromine in the dibromide is thus located at $C_{(18)}$ (VI; R = Me).

Like β-amyrin acetate, methyl *O*-acetyloleanolate absorbed one mol. of bromine in acetic acid to give the 12-bromo-derivative,* which more slowly took up a second mol. to give the 12 : 18-dibromide (VI; R = CO_2Me). Chromic acid oxidised the two bromides to the respective 11-ketones. Treatment of the dibromo-ketone (VII) with collidine resulted here in elimination of the elements of methyl bromide, producing in good yield a neutral, high-melting, methoxyl-free substance, the behaviour of which with alkali showed it to be a lactone. The band at 1890 cm.$^{-1}$ in the infrared spectrum indicated a γ-lactone, while the band at 1688 cm.$^{-1}$ and the maximum at 264 mμ in the ultraviolet

* In the less polar methylene chloride solution methyl *O*-acetyloleanolate reacts with bromine with participation of the methoxycarbonyl group to give the bromo-lactone.[7]

[6] Nussbaum, Mancera, Daniels, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1951, **73**, 3263.
[7] Corey and Ursprung, *ibid.*, 1956, **78**, 183; *Chem. and Ind.*, 1954, 1387.

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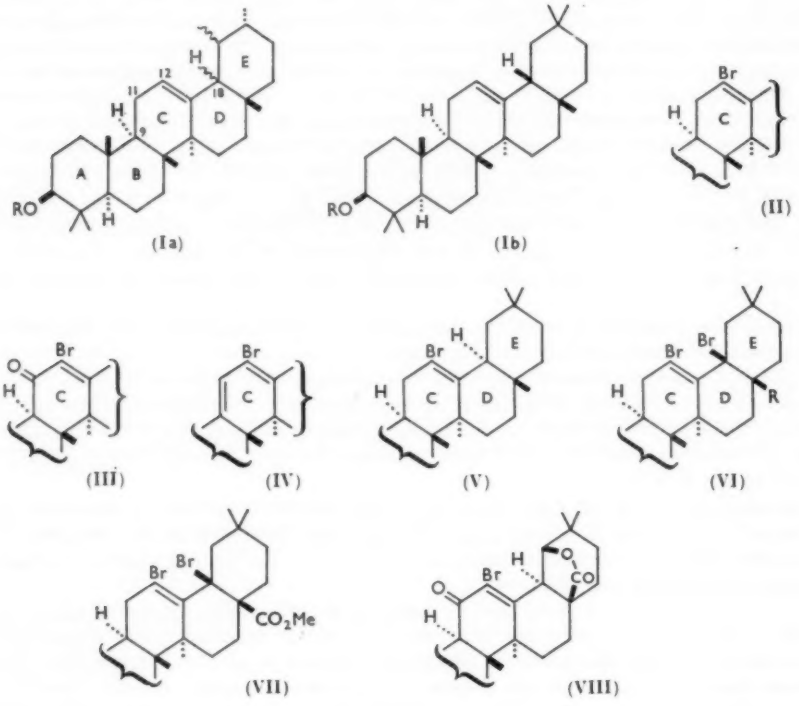
spectrum showed that the 12-bromo-12-en-11-one chromophore was probably still intact. These structural features are most simply accommodated by the tentative constitution (VIII).

The configuration of the 18-bromine atom in the dibromides is uncertain, but the nearly identical ultraviolet spectra of the mono- and di-bromides in both the long and the



short wavelength bands suggests very strongly that the 18-bromine is equatorial [8] to ring D (18β), rather than axial as might have been expected from the operation of purely electronic effects.[9]

Experimental

Optical rotations were measured in $CHCl_3$ (*c* 1—2%), and ultraviolet spectra in EtOH. Infrared spectra (in CS_2) were very kindly determined by Glaxo Laboratories Ltd.

12-Bromo-β-amyrin Benzoate.—β-Amyrin benzoate (3·52 g.), dissolved in dry carbon tetrachloride (70 ml.), was treated with bromine (10·2 ml. of 10·4% solution in acetic acid). The mixture was diluted with acetic acid (120 ml.) and then left in the dark for 5 hr. After filtration in benzene through alumina and three crystallisations from acetone the 12-bromo-derivative, isolated normally, melted constantly at 140—145° and then at 216—217° after resolidifying, and had $[\alpha]_D$ +44°, $\lambda_{max.}$ 229 mμ (ε 17,100) (Found : C, 72·6; H, 8·7; Br, 12·9. Calc. for $C_{37}H_{53}O_2Br$: C, 72·9; H, 8·8; Br, 13·0%). It gave a yellow colour with tetranitromethane in chloroform.

[8] Bird, Cookson, and Dandegaonker, *J.*, 1956, 3675.
[9] Corey, *J. Amer. Chem. Soc.*, 1954, **76**, 175.

12-*Bromo*-β-*amyrin Acetate*.—Bromine in acetic acid (6 ml. of 3% solution) was added to β-amyrin acetate (487 mg.) in carbon tetrachloride (20 ml.) and acetic acid (10 ml.). After 45 min. titration showed that one mol. of bromine had been taken up. The resulting bromo-derivative, filtered through alumina in benzene and recrystallised six times from chloroform–methanol, had m. p. 237—238°, $[\alpha]_D$ +44° (Found: C, 70·1; H, 9·3; Br, 14·8. Calc. for $C_{32}H_{51}O_2Br$: C, 70·2; H, 9·4; Br, 14·6%).

12 : 18-*Dibromo*-β-*amyrin Benzoate*.—Solutions of β-amyrin benzoate (3·0 g.) in carbon tetrachloride (20 ml.) and acetic acid (150 ml.) and of bromine in acetic acid (100 ml. of 3%) were mixed. After three days in the dark, reaction had ceased with the consumption of 2 mols. of bromine. The dibromide was filtered through alumina in benzene and recrystallised five times from chloroform–methanol to m. p. 214—215° (decomp.), $[\alpha]_D$ +50°, $\lambda_{max.}$ 230 mμ (ε 17,000), giving a yellow colour with tetranitromethane (Found: C, 64·2; H, 7·5; Br, 23·1. Calc. for $C_{37}H_{52}O_2Br_2$: C, 64·5; H, 7·6; Br, 23·2%).

12 : 18-*Dibromo*-β-*amyrin Acetate*.—Absorption of 2 mols. from an excess of bromine by β-amyrin under similar conditions gave the dibromo-acetate, m. p. 234—235° (decomp.), $[\alpha]_D$ +39°, after filtration through alumina in benzene and six recrystallisations from chloroform–methanol (Found: C, 61·6; H, 8·0; Br, 25·0. Calc. for $C_{32}H_{50}O_2Br_2$: C, 61·3; H, 8·0; Br, 25·5%).

12-*Bromo*-18α-β-*amyrin Acetate*.—18α-β-Amyrin acetate took up bromine much more slowly than the 18β-epimer. One mol. was absorbed in a few hours, and no more even in several weeks. The resulting 12-*bromide*, after chromatography and several recrystallisations from chloroform–methanol, had m. p. 218—219° (decomp.), $[\alpha]_D$ +47° (Found: C, 70·2; H, 8·9; Br, 14·8. $C_{32}H_{51}O_2Br$ requires C, 70·2; H, 9·4; Br, 14·6%).

Reduction of 12 : 18-*Dibromo*-β-*amyrin Acetate*.—The dibromide (1 g.) was treated with a large excess of zinc in boiling acetic acid for 3 hr. The product (820 mg.), recrystallised four times from chloroform–methanol, had m. p. 215—216° (decomp.), depressed by 12-bromo-β-amyrin acetate but not by 12-bromo-18α-β-amyrin acetate. The identity of the two compounds was confirmed by oxidation of each (see below) to the same 11-ketone (mixed m. p., identical rotations and spectra).

Dibromo-β-amyrin acetate was not affected by 24 hours' boiling in collidine, but when it was heated in collidine at 300° overnight the product yielded 12-bromo-18α-β-amyrin acetate (25%), m. p. and mixed m. p. 215—216° (decomp.) after chromatography and several recrystallisations.

12-*Bromo*-α-*amyrin Benzoate*.—α-Amyrin benzoate (2·46 g.) in carbon tetrachloride (30 ml.) and acetic acid (45 ml.) was treated with bromine in acetic acid (7·7 ml. of 10·4% solution). The mixture was worked up after 2 days, to give the bromo-ester as needles, m. p. 237—238°, $[\alpha]_D$ +65°, $\lambda_{max.}$ 229 mμ (ε 17,000), after filtration in benzene through alumina and four recrystallisations from chloroform–methanol (Found: C, 72·6; H, 8·5; Br, 13·4. Calc. for $C_{37}H_{53}O_2Br$: C, 72·9; H, 8·8; Br, 13·0%). It gave a yellow colour with tetranitromethane.

12-*Bromo*-α-*amyrin Acetate*.—α-Amyrin acetate (900 mg.) in carbon tetrachloride (20 ml.) and acetic acid (30 ml.), mixed with bromine in acetic acid (10 ml. of 3% solution), was left for one day. After filtration through alumina and three recrystallisations from chloroform–methanol the resulting bromo-derivative had m. p. 272—273°, $[\alpha]_D$ +66° (Found: C, 70·3; H, 9·2; Br, 14·5. Calc. for $C_{32}H_{51}O_2Br$: C, 70·2; H, 9·4; Br, 14·6%).

Hydrolysis of 12-bromo-α-amyrin benzoate by 10 hours' treatment with a 10% solution of potassium hydroxide in boiling diethylene glycol gave 12-bromo-α-amyrin, m. p. 177—178°, which gave the original acetate (mixed m. p.) on acetylation.

Debromination of 12-*Bromo*-β-*amyrin*.—Small pieces of sodium were added gradually to a solution of 12-bromo-β-amyrin benzoate (470 mg.) in boiling pentyl alcohol (20 ml.) until the solution became saturated (*ca.* 1½ hr.). The resulting β-amyrin had m. p. and mixed m. p. 195—196°, $[\alpha]_D$ +87°, after recrystallisation. The identity was confirmed by conversion of the alcohol into the acetate, m. p. 240—241°, not depressed by β-amyrin acetate.

Debromination of 12-*Bromo*-α-*amyrin*.—12-Bromo-α-amyrin benzoate, treated in the same way, gave α-amyrin, m. p. and mixed m. p. 184—185°, $[\alpha]_D$ +82°. Comparison of the corresponding acetate and benzoate with authentic α-amyrin esters confirmed the identity.

12-*Bromo*-11-*oxo*-β-*amyrin Benzoate*.—Solutions of 12-bromo-β-amyrin benzoate (700 mg.) in warm acetic acid (80 ml.) and of chromic oxide (350 mg.) in wet acetic acid (10 ml.) (*i.e.*, chromic oxide dissolved in the minimum of water, and the solution made up to 10 ml. with

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dry acetic acid) were mixed and kept at 82—85° for 40 min. The resulting 11-*ketone*, recrystallised thrice from chloroform–methanol, had m. p. 246—247°, $[\alpha]_D$ +54°, $\lambda_{max.}$ 230 (ε 15,000) and 269 mμ (ε 9500), $\nu_{max.}$ 1714 and 1678 cm.$^{-1}$; no colour with tetranitromethane (Found: C, 71·3; H, 8·0; Br, 12·65. $C_{37}H_{51}O_3Br$ requires C, 71·2; H, 8·2; Br, 12·8%).

12-*Bromo*-11-*oxo*-β-*amyrin Acetate*.—Chromic acid oxidised 12-bromo-β-amyrin acetate under the above conditions to the corresponding 11-*ketone*, m. p. 276—277°, $[\alpha]_D$ +51°, $\lambda_{max.}$ 269 (ε 10,000), 317 (ε 51), and 323—324 mμ (ε 54), $\nu_{max.}$ 1735 and 1680 cm.$^{-1}$, after three recrystallisations from chloroform–methanol (Found: C, 68·5; H, 8·8; Br, 14·25. $C_{32}H_{49}O_3Br$ requires C, 68·4; H, 8·8; Br, 14·25%). This acetate could also be made by hydrolysis of the benzoate with potassium hydroxide in methanol–benzene, followed by acetylation.

12-*Bromo*-11-*oxo*-18α-β-*amyrin Acetate*.—Oxidation of 12-bromo-18α-β-amyrin acetate with chromic acid in acetic acid gave the 18α-11-*ketone*, m. p. 263—264°, $[\alpha]_D$ 49°, $\lambda_{max.}$ 267 mμ (ε 9050) (Found: C, 68·8; H, 8·7; Br, 14·25. $C_{32}H_{49}O_3Br$ requires C, 68·4; H, 8·8; Br, 14·25%).

Reduction of 12 : 18-*Dibromo*-11-*oxo*-β-*amyrin Acetate*.—The dibromo-ketone (200 mg.) in redistilled collidine (6 ml.) was heated at 300° for 24 hr. After chromatography and recrystallisation from chloroform–methanol the product (100 mg.) had m. p. 261—262°, alone and mixed with 12-bromo-18α-β-amyrin acetate, $[\alpha]_D$ 48°, $\lambda_{max.}$ 267 mμ (ε 9100).

12-*Bromo*-11-*oxo*-α-*amyrin Benzoate*.—This *compound*, recrystallised thrice from chloroform–methanol, had m. p. 252—253°, $[\alpha]_D$ +100°, $\lambda_{max.}$ 230 (ε 15,000) and 269—270 mμ (ε 9700), no colour with tetranitromethane (Found: C, 71·0; H, 7·9; Br, 12·8. $C_{37}H_{51}O_3Br$ requires C, 71·2; H, 8·2; Br, 12·8%).

12-*Bromo*-β-*amyra*-9(11) : 12-*dien*-3β-*yl Acetate*.—A solution of 12-bromo-11-oxo-β-amyrin benzoate (890 mg.) in dry benzene (5 ml.) and ether (30 ml.) was added to lithium aluminium hydride (450 mg.) in ether (110 ml.). The mixture was boiled for 45 min. and the crude isolated product was then boiled for 3 hr. with acetic anhydride (10 ml.) containing toluene-*p*-sulphonic acid (*ca.* 15 mg.). The resulting *bromo-diene*, after filtration in benzene through alumina and four recrystallisations from chloroform–methanol, had m. p. 213—214°, $[\alpha]_D$ +206°, $\lambda_{max.}$ 282—283 mμ (ε 9500) (Found: C, 70·2; H, 8·85; Br, 15·0. $C_{32}H_{49}O_2Br$ requires C, 70·4; H, 9·05; Br, 14·7%). It gave a deep brown colour with tetranitromethane in chloroform.

12-*Bromo*-α-*amyra*-9(11) : 12-*dien*-3β-*yl Acetate*.—Reduction, dehydration, and acetylation of 12-bromo-11-oxo-α-amyrin benzoate as for the β-amyrin derivative afforded the *bromo-diene*, which was recrystallised four times from chloroform–methanol. It then had m. p. 212—213°, $[\alpha]_D$ +229°, $\lambda_{max.}$ 282—283 mμ (ε 9200) (Found: C, 70·4; H, 8·8; Br, 14·9. $C_{32}H_{49}O_2Br$ requires C, 70·4; H, 9·05; Br, 14·7%). It gave a deep brown colour with tetranitromethane in chloroform. It was unchanged by bromine in acetic acid at 90°.

Debromination of 12-*Bromo*-9(11) : 12-*dienes*.—A solution of 12-bromo-β-amyra-9(11) : 12-dien-3β-yl acetate (400 mg.) in boiling *n*-pentyl alcohol (20 ml.) was saturated with small pieces of sodium during 1 hr. After acetylation, the crude product was filtered through alumina in benzene. Four recrystallisations produced crystals, m. p. 215—216°, $[\alpha]_D$ +335, $\lambda_{max.}$ 282 mμ (ε 9800), which had the same m. p. when mixed with β-amyra-9(11) : 12-dien-3β-yl acetate. The m. p.s of the derived alcohol, 211—212°, and benzoate, 248—249°, were also undepressed by genuine samples.

Reduction of 12-bromo-α-amyra-9(11) : 12-dien-3β-yl acetate in the same way led to α-amyra-9(11) : 12-3β-yl acetate, m. p. and mixed m. p. 166—167°, $[\alpha]_D$ +305°.

12 : 18-*Dibromo*-11-*oxo*-β-*amyrin Benzoate*.—(a) *From* 12 : 18-*dibromo*-β-*amyrin benzoate*. 12 : 18-Dibromo-β-amyrin benzoate (200 mg.) in acetic acid (50 ml.) was oxidised at 82—85° with chromic oxide (100 mg.) in wet acetic acid (5 ml.). After 30 min. the mixture was worked up. The *dibromo-ketone* melted at 253—254° (decomp.) after four recrystallisations from chloroform–methanol, and had $[\alpha]_D$ +59°, $\lambda_{max.}$ 230 (ε 17,000) and 269 mμ (ε 10,200) (Found: C, 63·2; H, 7·1; Br, 22·75. $C_{37}H_{50}O_3Br_2$ requires C, 63·2; H, 7·2; Br, 22·8%).

(b) *From* 12-*bromo*-11-*oxo*-β-*amyrin benzoate*. Bromine in acetic acid (3 ml. of 3% solution) was added drop by drop to a solution of 12-bromo-11-oxo-β-amyrin benzoate (234 mg.) in acetic acid (60 ml.) at *ca.* 90° during 30 min. Having been left for another hour at 90° the mixture was worked up. The product was filtered through alumina in benzene and recrystallised twice from chloroform–methanol, to give the dibromo-ketone, m. p. 252—253° (not depressed by the above sample), $[\alpha]_D$ +61°, $\lambda_{max.}$ 230 (ε 17,800) and 268 mμ (ε 10,500), $\nu_{max.}$ 1714 and 1682 cm.$^{-1}$.

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12 : 18-Dibromo-11-oxo-β-amyrin benzoate was recovered unchanged after 3 hours' boiling with hydrogen bromide in acetic acid, or 1½ hours' boiling with collidine.

12 : 18-*Dibromo*-11-*oxo*-β-*amyrin Acetate.*—Oxidation of 12 : 18-dibromo-β-amyrin acetate as for the benzoate gave the 11-*oxo-acetate*, m. p. 247—248° (decomp.) (after six recrystallisations from chloroform–methanol), $[\alpha]_D$ +51°, $\lambda_{max.}$ 269 (ε 10,500) and 320—321 mμ (ε 58) (Found : C, 60·3; H, 7·6. $C_{32}H_{48}O_3Br_2$ requires C, 60·0; H, 7·55%).

An identical acetate (mixed m. p., ultraviolet spectrum, and rotation) was produced by hydrolysis of the corresponding benzoate and acetylation.

β-*Amyra*-9(11) : 12 : 18-*trien*-3β-*yl Acetate.*—A solution of 11-oxo-β-amyra-12 : 18-dien-3β-yl benzoate (270 mg.) in ether (200 ml.) was added to one of lithium aluminium hydride (500 mg.) in ether (100 ml.). After an hour's boiling the crude, isolated product was boiled for 3 hours in acetic anhydride (5 ml.). The resulting β-amyra-9(11) : 12 : 18-trien-3β-yl acetate was purified by filtration in benzene through alumina and six recrystallisations from chloroform–methanol. It then showed m. p. 180—181°, $[\alpha]_D$ +510°, $\lambda_{max.}$ 308 mμ (ε 13,500). A sample of the triene made by dehydrogenation of β-amyrin acetate with *N*-bromosuccinimide had almost identical physical properties and a mixture of the two samples had the same m. p.

Bromination of 11-*Oxo*-β-*amyrin Benzoate.*—The ketone (580 mg.), dissolved in chloroform (10 ml.), was treated with bromine in acetic acid (50 ml. of 4·2% solution) in the presence of hydrogen bromide (10 drops of 50% solution in acetic acid). A week later the mixture was worked up, to yield a *dibromo-ketone*, which after four recrystallisations from chloroform–methanol melted first at 215° and then at 234—235° (decomp.) and had $[\alpha]_D$ +455° and $\lambda_{max.}$ 230 (ε 22,000) and 272 mμ (ε 8200) (Found : C, 63·1; H, 6·85; Br, 21·3. $C_{37}H_{50}O_3Br_2$ requires C, 63·2; H, 7·2; Br, 22·8%).

Methyl O-*Acetyl*-12-*bromo-oleanolate.*—Methyl *O*-acetyloleanolate (1·55 g.) in dry carbon tetrachloride (20 ml.) and acetic acid (100 ml.) was treated with bromine in acetic acid (16 ml. of 3% solution). After 1½ hr. one mol. of bromine had been consumed and the mixture was worked up normally. The 12-*bromo-derivative* was filtered through alumina in benzene and recrystallised twice from chloroform–methanol to m. p. 217—218°, $[\alpha]_D$ +32°, yellow with tetranitromethane (Found : C, 66·9; H, 8·6; Br, 13·4. $C_{33}H_{51}O_4Br$ requires C, 66·9; H, 8·7; Br, 13·5%).

Methyl O-*Acetyl*-12 : 18-*dibromo-oleanolate.*—Solutions of methyl *O*-acetyloleanolate (1·09 g.) in carbon tetrachloride (50 ml.) and acetic acid (125 ml.) and of bromine in acetic acid (50 ml. of 2% solution) were mixed. After three days two mols. of bromine had been absorbed. The *dibromo-derivative*, isolated as usual, was filtered in benzene through alumina and recrystallised four times from chloroform–methanol. It then had m. p. 210—212° (decomp.) and $[\alpha]_D$ +38°, and gave a yellow colour with tetranitromethane (Found : C, 59·0; H, 7·3; Br, 23·6. $C_{33}H_{50}O_4Br_2$ requires C, 59·0; H, 7·5; Br, 23·8%).

Methyl O-*Acetyl*-12-*bromo*-11-*oxo-oleanolate.*—Methyl *O*-acetyl-12-bromo-oleanolate (700 mg.) in acetic acid (50 ml.) was treated with chromic oxide (500 mg). in water (3 drops) and acetic acid (3 ml.). The mixture was heated on the steam-bath for 45 min. and the isolated product was filtered through alumina in benzene and recrystallised four times from chloroform–methanol. The *bromo-ketone* then had m. p. 276—277°, $[\alpha]_D$ +62°, $\lambda_{max.}$ 268—269 mμ (ε 10,500), no colour with tetranitromethane (Found : C, 65·15; H, 8·1; Br, 13·7. $C_{33}H_{49}O_5Br$ requires C, 65·4; H, 8·1; Br, 13·2%).

Methyl O-*Acetyl*-12 : 18-*dibromo*-11-*oxo-oleanolate.*—Oxidation of methyl *O*-acetyl-12 : 18-dibromo-oleanolate with chromic acid as above gave the *dibromo-ketone*. After filtration through alumina in benzene and four recrystallisations from chloroform–methanol it had m. p. 230° (decomp.) and then *ca.* 260° after re-solidifying, $[\alpha]_D$ +54°, $\lambda_{max.}$ 269 mμ (ε 11,000) (Found : C, 58·0; H, 6·9; Br, 23·0. $C_{33}H_{48}O_5Br_2$ requires C, 57·9; H, 7·1; Br, 23·3%).

Action of Collidine on Methyl O-*Acetyl*-12 : 18-*dibromo*-11-*oxo-oleanolate.*—The dibromo-ester (180 mg.) was heated with freshly distilled collidine (2 ml.) at 200° for 16 hr. The resulting *bromo-lactone* (140 mg.), crystallised twice from methanol, had m. p. 325—326° (decomp.), $[\alpha]_D$ −23°, $\lambda_{max.}$ 263—264 mμ (ε 10,000), $\nu_{max.}$ 1790, 1730, and 1688 cm.$^{-1}$ (Found : C, 65·3; H, 7·8; Br, 13·6. $C_{33}H_{45}O_5Br$ requires C, 65·2; H, 7·7; Br, 13·6%).

Methyl *O*-acetyl-12-bromo-11-oxo-oleanolate was unchanged by collidine under the same conditions.

Pyrolysis of Methyl O-*Acetyl*-12 : 18-*dibromo*-11-*oxo-oleanolate.*—The dibromo-ester was

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heated at 230—235° and room pressure for 5 min. Two crystallisations of the product from methanol gave the bromo-lactone, m. p. 321—322° (decomp.), $[\alpha]_D$ −21·5°, $\lambda_{max.}$ 263—264 mμ (ε 10,000): mixed with the sample made with collidine, it had m. p. 324—325° (decomp.).

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190. *The Separation of the Lanthanons with the Aid of Ethylenediaminetetra-acetic Acid ("Enta Acid"). Part VI.* Ion-exchange Studies of the Heavy and Middle Lanthanons and Yttrium.*

By J. K. MARSH.

Hot, shallow beds of fine sulphonated polystyrene cation exchanger are loaded with lanthanons and developed on a bed of mixed copper and hydrogen forms of the resin by elution with ammonium-buffered "enta acid". Good yields of purified heavy and middle lanthanons are obtained, but the separation of dysprosium from yttrium is exceptionally difficult.

A crude load of 0·6 equivalent of lanthanon per cm.² of column cross-section on a bed 60 cm. deep was separated into ternary mixtures. These, re-run at 0·1—0·15 equiv./cm.², were resolved satisfactorily on 45- or 60-cm. beds (load vol./development vol. = 1) and recovered in solution of concentrations greater than 0·2 equiv./l. Intermediates between each pair of purified earths amounted to about 0·007 equiv./cm.² or a 3 cm. band on the developed column.

THE main factors governing the use of ion-exchange resins for separating elements by complex-forming eluants are well established. Thus, the lanthanons have been successfully separated on columns about 10 cm. long of very fine resin near 100° with tracer loads, or again with resin of commercial grade at air temperature, on columns[1] totalling 25—30 m. and 1000 l. in volume with loads of about 0·8 equiv./cm.². Large plants of similar design are now in use, but intermediate designs have also been described. Spedding, Powell, and Wheelwright[2] eluted copper and lanthanons successively from 90-cm. columns each with fillings of −80 to +175 mesh (British) of sulphonated polystyrene resin, using as eluant 2% enta acid in aqueous ammonia solution at pH of 8—9. French workers at C.N.R.S., Bellevue, used sulphonated polystyrene beads in the hydrogen form, of commercial size, in 6—9 m. of columns and eluted with buffered enta acid solutions at the low concentrations necessitated by the small solubility of the free enta acid which is liberated by complex formation of the lanthanons.[3]

The present work follows most nearly the technique of development with copper, which is combined with that in which the hydrogen bed is used. Fine resins have been used and the temperature was raised so that viscosity was lowered and the rate of exchange raised. The columns may thus be shortened, and the plant and resin requirement kept small for a given output. Scaled up for industrial operation, the short columns would be replaced by broad beds.

For about four months, use of copper development columns gave results at least as good as those of Spedding, Powell, and Wheelwright,[2] but then suddenly a complex copper enta salt of low solubility appeared, and the process became unworkable. Only limited

* Part V, *J.*, 1955, 451.

[1] Spedding and Powell, *Chem. Eng. Progr. Symp.*, 1954, **50**, 7.
[2] Spedding, Powell, and Wheelwright, *J. Amer. Chem. Soc.*, 1954, **76**, 2557.
[3] Loriers and Quesney, *Compt. rend.*, 1954, **239**, 1643; Berghezan and Hérenguel, *ibid.*, 1955, **240**, 1537; Loriers, *ibid.*, 1956, **242**, 261; see also Topp, *Chem. and Ind.*, 1956, 1320.

supersaturation was thenceforth obtainable. Various additives were tried with the object of maintaining supersaturation; the best was a few per cent. of sucrose. It has been found, however, that a mixed copper and hydrogen developing column allows of smooth working. Analysis of the insoluble copper salt indicates the composition Cu[Cu enta],$5H_2O$, though copper was low and hydrogen high pointing to considerable uptake of the soluble dibasic cupric–enta acid, H_2[Cu enta]. Since H_4 enta is also nearly insoluble it is obvious that the eluate during the development stage should be the above soluble cupric–enta acid. The lanthanon (Ln) being assumed to move as Ln enta^{1-}, this will result from the reaction:

$$\text{Ln enta}^{1-} + \text{CuR}_2 + \text{HR} \longrightarrow \text{LnR}_3 + \text{H}_2\text{Cu enta}$$

In practice a mixture of two parts of copper resin and one part of hydrogen resin was found to be the most satisfactory. However, under working conditions there is a tendency for hydrogen to run off too quickly so that late copper eluates show a deeper colour and higher pH and there is a risk of deposition of Cu[Cu enta] causing a blockage in the outlet or a blurring of the copper–lanthanon boundary. If too much hydrogen is present when the elution of copper finishes trouble may ensue owing to crystallisation of free enta acid.

Yttrium presents a special case in that it has to be interpolated in the lanthanon series without occupying a space of its own. In normal complex elution it comes close to dysprosium, but when very dilute eluants are used it may not run off till after terbium.[4] Loriers and Quesney [3] from material containing 90% of yttrium, using a loading of only 0·03 equiv./cm.^{2}, obtained 25% of the yttrium as the trioxide (over 99·9% pure) in solution of concentration less than 1·5 g./l. Yttrium of 99% purity is comparatively easily prepared by methods other than ion-exchange, so that material of this purity was used by us. It was confirmed that load and eluant concentration must be kept low, though after development with a dilute solution it was found possible to recover the yttrium by use of eluant of usual concentration. The ion-exchange purification of dysprosium has not been investigated.

Since the light lanthanons give insoluble octahydrated ammonium lanthanon enta salts, a slight white deposit is often seen at the rear of a heavy lanthanon elution. If there is a considerable light lanthanon content in the load separations are adversely affected.

Experimental

Apparatus.—A glass-fibre insulated hot chamber (controlled by thermostat) above a time-based fraction collector held the loaded resin container and the developing column, usually a standard 2 in. Pyrex industrial pipe, 18 or 24 in. long, fitted at the bottom with a felt pad on a perforated glass plate. Hydrostatic pressures up to 4 m. of water were available. The eluate was warmed by being kept in the chamber for a sufficient time before contact with the resin. A time switch provided predetermined operation of heating and eluant flow. It was often convenient to start the elution automatically during the night; for this a rubber tube in the eluant supply line was pinched shut by the loop end of a small tension spring passing through the shelf on which the tube rested. The spring was stretched by a 1 amp. fuse wire which melted when the time switch operated. If the electricity supply failed, a bar was allowed to fall on the tube, thus stopping the flow of eluant. For the collection of fractions, the eluant passed from the hot chamber by a glass ball joint and thence through a stainless steel spindle, to a delivery arm (1/16 in. bore stainless steel) which revolved above a circular rack (radius 15 in.) of 90 holes (diam. $\frac{7}{8}$ in.) which took test tubes for fractions up to 35 c.c. or small funnels delivering into 12 oz. (340 c.c.) medicine bottles. The delivery arm was driven by an electric clock movement through gears at 8—32 min./hole. The delivery arm terminated in a rubber tube inside a spring to which was attached a flag which made contact with a peg beside each hole, thus keeping the tube over the hole until the rotation caused it to jump to the next one. For large-scale work the outputs from groups of four holes each were delivered into larger

[4] Spedding, *J. Amer. Chem. Soc.*, 1950, **72**, 5350; Loriers and Quesney, ref. 3.

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vessels. The fraction collector has thus a very wide range, but in this work flow rates of 10—20 c.c./min. have been used, and collection of fractions in medicine bottles at 15—24 min. intervals has been most general.

Resin.—Dowex 50, −250 + 500 mesh, resin was used. Fine material was removed by extensive fractional sedimentation and the remainder was further graded into four grain sizes. Grade 1, the coarsest 40% of the total resin, was used for loading with the lanthanon charge, and grades 2 (30%) and 3 (20%) for the developing columns. Grade 4 was too fine for general use, and grade 3 was best suited for use in columns not longer than 45 cm. Close grading of the resin leads to even filling of the columns and to high efficiency by reducing the amount of channelling under large hydrostatic heads. Much of grade 1 proved to be over 250 mesh size. An approximate balance was found between mesh size, hydrostatic head, and exchange efficiency. Thus if a 60 cm. column of a resin required a given head for a given flow rate a 30 cm. column of finer resin giving the same flow rate under the same head would give an equally good separation at the same loading per c.c. of development bed (*i.e.*, half the first load). Even with these fine resins and high temperatures approximate equilibrium working is obtained only with flow rates below 0·5 cm./min. If we allow that the eluate in the resin bed occupies 40% of the volume, it will then traverse less that 1·25 cm. of bed/min.

General Operation.—Standard 2 in. Pyrex industrial pipes were used as developing columns, after trials with smaller columns. The lanthanon charge was usually held in a cylinder of 2 l. capacity and 62 cm.^{2} cross section, fitted in the lower conical part with a coarse sintered glass disc (diam. 5 cm.). A 6 l. aspirator bottle of 230 cm.^{2} cross section with 2 in. pipe-end neck was also used as charge container for rough separations of large quantities; good separation required that the volume of lanthanon-charged resin should not exceed the volume of developing resin, but a two-stage separation of a crude material is generally profitable. The first-stage eluates are acidified to 0·5N with hydrochloric acid and the precipitated H_4 enta removed after 2—3 days' standing. The earth contents are then reabsorbed on resin for the second stage of purification. It is best, however, to finish the charging of the resin from a neutral solution. The first stage allows grouping of the elements into products having three main constituents, and the second stages treat these groups separately to give high yields of pure products. Pure materials can be prepared with intermediates amounting to at most 0·4 g./cm.^{2} of column, or a 3 cm. band of developed resin bed. Since the total load is of the order of 6—8 g./cm.^{2}, only small pure crops are obtainable if numerous elements are present, and none for earths constituting less than 6—8% of the mixture.

As stated previously the aim during the development period is to run off H_2Cu enta. If this is not achieved blockages may occur, usually in the delivery arm or at its tip; such crystallisation was avoided by adjusting the pH of the eluate as it left the column by introducing acid or ammonia solution through a hypodermic needle in the rubber gasket below the pipe-end. Good separations are obtained when, during the lanthanon elution, the natural acidity is such that considerable H_4 enta crystallisation occurs on standing, but sometimes a crust forms and stops the flow where evaporation is high at the delivery tip.

Eluants containing 2% of H_4 enta buffered with ammonia to pH 8·8 (thymol-blue capillator test), *i.e.*, corresponding approximately to $(NH_4)_3H$ enta, have been used, generally made up from demineralised Thames water. The eluates have pH <2·5 (*i.e.*, in the red range of thymol-blue) if there is no danger of Cu_2 enta formation. Provision was made at the top of the column to permit the escape of gas. Above 70° a slow formation of gas in the resin bed occurred, which caused poor results and limited the desirable duration of a run to 40 hours. Partial degassing of solutions is therefore desirable, but temperatures over 70° were not generally used. The resin changes colour on passing from the copper to the lanthanon form with a sharp horizontal boundary, an advance of which of 3—4 cm./hr. is suitable. Thus a 60 cm. column of copper followed by an equal volume of lanthanon will be eluted in 30—40 hours.

In the following accounts of particular experiments the general conditions were as already indicated unless otherwise specified. All weights are given as the oxides (Ln_2O_3).

Crude Heavy-earth Concentrate derived from Gadolinite.—Much of the yttrium had been eliminated by the basic nitrate process. 5 l. of grade 1 resin, loaded with lanthanons (12 equiv.) to give a bed 18 cm. deep, were separated by a felt diaphragm from a 60 cm. × 21 cm.^{2} column of grade 3 resin, half in the copper and half in the hydrogen form. The whole was eluted with 1·5% of H_4 enta in ammonia solution at pH 8·8 until lanthanons appeared (24 hr.) and then 2% of H_4 enta in ammonia solution at pH 8·8 and 80°. Fractions 1—105 were collected at

16 min. intervals, 106—118 at 128 min. intervals. Spectrometry in 1 cm. cells showed Yb in 1—45 (max. 40), Tm in 35—105 (max. 45), Er in 50—111 (max. 85), Ho in 85—118 (max. 113), Dy in 109—118 (max. 115). After 72 hours the charge-bottle was disconnected and the column eluted to completion. The remaining charge (70 g.) was developed subsequently on another column; the first few fractions contained a little holmium but over 10% of dysprosium, dropping to 0·2% at the tail which appeared to contain nearly pure yttrium, with only a small amount of terbium in the last fraction.

In the main experiment gas development was excessive owing to too high a temperature and too prolonged an elution, but four useful concentrates were obtained, *viz.*, (*a*) pre-erbium, (*b*) erbium, (*c*) holmium, and (*d*) dysprosium–yttrium. The crude erbium was re-run first, giving heads and tails to increase (*a*) and (*c*). Most of the ytterbium was removed from the pre-erbium concentrate by the sodium amalgam process before further ion-exchange treatment.

Purification of erbium. 1·25 l. of grade 1 resin in the erbium form in a 62 cm.² bed over a development column (60 cm. × 21 cm.²) of grade 2 resin ⅔rds. in the copper and ⅓rd. in the hydrogen form were eluted with a 2% solution of H_4enta at pH 8·7 at 70—75°. Fractions (250—215 c.c.), collected at 16 min. intervals contained: 1—10, no erbium; 1—17, some Tm; 18—64, pure Er (Er_2O_3, 127 g.); 65—72, Er and Ho; 73, pure Ho. The tail (76) contained 7% of Dy and 37% of Ho.

Purification of holmium. 650 c.c. of grade 1 resin in the holmium form in a 62 cm.² bed over a development column (45 cm. × 21 cm.²) of grade 2 resin as above were eluted with the same solution at 15—65°. About 33 cm. of the development column were eluted cold unintentionally, and the adverse effect on the elution is evident. Fractions contained: 1—4, mainly Cu with some Er; 5, a little Ho; 6—9 (9·7 g.), mainly Ho; 10—13 (10 g.), trace of Er; 14—25 (30 g.) pure Ho; 27, impure (50%) Ho.

Purification of lutetium and thulium. 900 c.c. of grade 1 resin in the mixed lanthanon form over a development column (60 cm. × 21 cm.²) of grade 2 resin as above were eluted with the same solution at 70°, at a rate of 12 c.c./min. Fractions collected at 15 min. intervals contained: 1—14, Lu (25·2 g.) and a trace of Sc (Yb was not detected by arc spectroscopy by Johnson, Matthey and Co. Ltd.); 15—20, Lu + Yb (12·2 g.); 21—24, Yb (8·4 g.); 25—28, Yb + Tm (8·2 g.); 29—56, Tm (52·7 g.) and 0·04% of Yb (Er was not detected by arc spectroscopy as above); 57—62, Tm + Er (11 g.), 63—67, Er (9 g.); 68—72, Er + Ho + Dy (6·5 g.).

Purification of gadolinium. Crude gadolinium was prepared from ore by two double sodium sulphate precipitation (cf. ref. 5, Table 2, fraction 6) (Found: Pr, 1; Nd, 9; Sm, 26; Eu + Gd + Tb, 50; Dy, 5; Y, 9%). This was used to transform grade 1 resin into the lanthanon form, 800 c.c. of which in a 62 cm.² bed over a development column (45 cm. × 21 cm.²) of grade 2 resin as above were eluted with the above solvent at 65—67°. Fractions collected at 19·2 min. intervals contained: 1, Er (13) + Ho (13) + Dy (71) + Y (3%); 2, Dy (94) + Y (6%); 3, Dy (93) + Y (7%); 4, Dy (30) + Y (70%) (total 1—4, 7·6 g.); 5—6, Dy (0·7) + Y (99·3%) (total 3·2 g.); 7—11, Y (7·4 g.); 12—15, Y + Tb + Gd (8·2 g.); 16—32, Gd (40·5 g.); 33, Gd (96) + Eu (4%); 34, Gd (49) + Eu (35) + Sm (16%); 35, Gd (8) + Eu(14) + Sm (18) (total 33—35, 8·5 g.); 36—44, Sm (21·6 g.); 45—49, Sm + Nd (8·8 g.); 50, Nd (1·6 g.); 51—52, Nd + Pr + La (5 g.).

Purification of terbium. 1·1 l. of grade 1 resin in the terbium form in a 62 cm.² bed over a development column (60 cm. × 21 cm.²) as above were eluted with a 2% solution of H_4enta in ammonia at pH 8·8 (15 l.) at 60—65°, for 21 hr. A total of 10 l. of eluant was collected in 61 fractions at 19·2 min. intervals, and contained: 1—8, white oxides free from Tb, mostly Dy and Y; 9, cream-coloured oxide: 10, ochre oxide; 11—50 (Tb_4O_7, 100 g.), oxides of uniform colour, of which those in 12 and 50 were shown by arc spectroscopy not to contain Dy or Gd (Johnson, Matthey and Co. Ltd.). Terbium was absent from fraction 55, which contained pure Gd.

Purification of yttrium (from 99·2%). 550 c.c. of grade 1 resin in the yttrium form in a 62 cm.² bed over a development column (60 cm. × 21 cm.²) as above were eluted for the first 65 cm. with a 1·25% solution (pH 8·4) and thereafter a 2% solution (pH 8·7) of H_4enta in aqueous ammonia at 68°. Development for 30 hr. consumed 23 l. and was followed by 29 fractions at 24 min. intervals containing in all 45 g. in 7·3 l. or 0·06 equiv./cm.³. Fractions contained: 1, Dy (13·5) + Ho (6·1) + Er (9·7%) (total 0·8 g.); 3, Dy (1·25) + Ho (0·17) + Er (0·06%) (total 1·8 g.); 6, Dy (0·5%); 8—9, Dy (0·1%); 10—11, Dy (0·05%); 12—28, Dy (0%) (total 27 g.). At the low concentrations dysprosium was estimated spectrophotometrically

[5] Marsh, *J.*, 1952, 4804.

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through 4 cm. of a solution of Y_2O_3 (250 g./l.) in hydrochloric acid. If Beer's law holds, the sensitivity was 0·01% of Dy_2O_3. With heavier loads in other experiments it was found that the head fractions showed large concentrations of impuriries, and the tails were of high purity, but there was a long central portion which was of approximately the same composition as the input. Even in the last experiment fractions 4—6 showed little change in dysprosium content and were of approximately input composition.

Purification of neodymium. A high yield of high-purity neodymium was obtained from a mixture containing 88% of Nd and 12% of Pr by using, in a single column, 30 cm. of Cu-resin and 15 cm. of Nd-resin, a 50% increase in elution rate, a lower temperature (55°), and the usual 2% enta-acid eluant. The short duration of the elution prevented growth of large insoluble particles in the column.

Purification of praseodymium. Addition of 1% of hydroxyethylethylenediaminetriacetic acid (HEDTA) to the usual 2% enta-acid at the same pH served to delay the formation of insoluble enta salts. A 90 c.c. load (Pr 88; Nd 0·5%) on a 45 cm. × 2·5 cm.^{2} Cu-resin column eluted at 40° contained all the neodymium in the first 4% of the lanthanon runnings. The eluant was then changed to a mixture of 0·65% enta-acid and 1·3% HEDTA at pH 8·8, since the stability constants of the lanthanum and praseodymium complexes [6] indicate the superiority of HEDTA for the separation of this pair. Also HEDTA has the advantage of yielding soluble complexes. A sharp separation of Pr from Ce and La resulted.

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, July 10th*, 1956.]

[6] Spedding, Powell, and Wheelwright, *J. Amer. Chem. Soc.*, 1956, **78**, 34.

191. *Electron-donor and -acceptor Complexes with Aromatic Systems. Part V.* Polarisation Bonding in Solid Complexes formed by Some Heterocyclic Aromatic Molecules.*

By W. SLOUGH and A. R. UBBELOHDE.

Solid complexes formed by various benzoquinolines with sodium or bromine have been prepared. All the benzoquinolines studied can apparently act either as donors or acceptors of electrons. From the behaviour of the different structures when bonded with a typical electron donor such as sodium or an acceptor such as bromine, the gradation from strongest donor to strongest acceptor properties appears to be in the sequence 2 : 3-benzoquinoline (acridine), 3 : 4-benzoquinoline (phenanthridine), 5 : 6-benzoquinoline, 7 : 8-benzoquinoline.

Methods for preparing the sodium complexes include new findings relating to enrichment by vacuum sublimation. Comparatively easy reversibility of complex formation with bromine permits approach to any desired composition from either side by direct addition or removal of bromine. Density measurements show marked electrostriction on formation of a typical sodium complex. With bromine, the degree of electrostriction with different benzoquinolines depends on the relative acceptor–donor character.

As the proportion Br : aromatic compound rises, there is an anomalous variation of excess of volume suggesting that in a solid complex, dimer formation occurs for low bromine ratios.

Complex formation of the benzoquinolines with either bromine or sodium enhances the electrical conductivity of the solids, which behave as semiconductors. Conductance is non-ohmic at the higher current densities. Systematic information has been obtained on the trend of the parameters σ_0 and E in the conductance–temperature relation $\log \sigma = \log \sigma_0 - E/\boldsymbol{k}T$ as the proportion of heterocyclic molecule in a complex is altered.

The significance of these results is discussed in the light of current theories of the electronic structure of aromatic molecules, and of polarisation bonding in relation to aromatic structure.

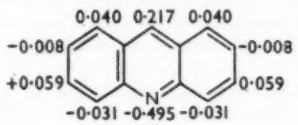
THE extension of the chemical physics of aromatic systems requires systematic experimental information on the electronic characteristics of groups of closely related structures.

* Part IV, *J.*, 1957, 918.

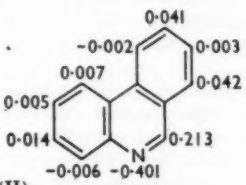
Experimental progress in this direction is often limited by the unavailability of substances whose structure is of key importance in a group, and theoretical knowledge is often scanty about comparative electron affinities and ionisation energies and about energy levels near the ground states in related aromatic systems. Such considerations limit the choice of systems suitable for quantitative studies. Charge-transfer bonding in solution can be conveniently studied, for example, by means of ultraviolet absorption spectra. Differences in the absorption bands for related aromatic molecules can to some extent be related with the parameters already referred to. In the solid state additional information about the nature of the bonding can be obtained from the molar volumes of the complexes and their electronic conductances. Previous papers [1,2,3] have discussed the quasi-metallic bonding in solid complexes of aromatic hydrocarbons with electron donors such as the alkali metals, or electron acceptors such as bromine. Solid bromine complexes have also been described.[4,5]

We now deal with electronic and related properties of solid complexes formed by a group of heterocyclic analogues of anthracene and phenanthrene (I)—(IV). The net charges shown are due to Coulson and Longuet-Higgins.[6]

Introduction of one nitrogen atom into an aromatic system is well known to facilitate its acting as an electron acceptor; for example, pyridine forms addition complexes with sodium much more readily than benzene. As is described below, various addition complexes have been prepared between sodium and 2 : 3 (I)-, 3 : 4 (II)-, 5 : 6 (III)-, and 7 : 8 (IV)-benzoquinolines. 6 : 7-Benzoquinoline was not available and has previously only been synthesised with difficulty in very low yield. The benzoquinolines form solid



(I)



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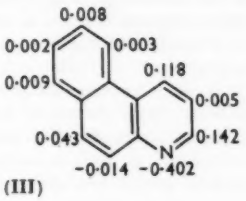

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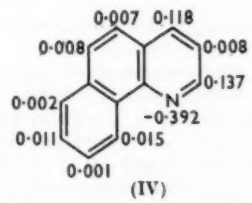
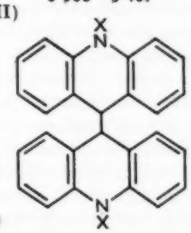
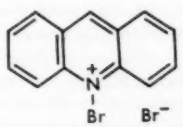


(IV)



(V)



(VI)

addition complexes with bromine without rapid nuclear substitution of bromine, unlike their hydrocarbon analogues under comparable conditions. Measurements here recorded permit comparisons of the electron donor and acceptor properties of the same molecule, for an interesting diversity of complexes.

Experimental

Nitrogen (British Oxygen Co. " white-spot "), which originally contained less than 20 p.p.m. of oxygen, was further freed from oxygen by passage through a 100 cm. column tightly packed with copper turnings, the surface of which was constantly renewed by scrubbing it with ammonia solution (*d*, 0·880). The issuing gas was passed through a column packed with glass beads

[1] McDonnell, Pink, and Ubbelohde, *J.*, 1951, 191.
[2] Holmes-Walker and Ubbelohde, *J.*, 1954, 720.
[3] Gracey and Ubbelohde, *J.*, 1955, 4089.
[4] Acheson, Hoult, and Barnard, *J.*, 1954, 4142.
[5] Akamatu, Inokuchi, and Matsunaga, *Nature*, 1954, **173**, 168.
[6] Coulson and Longuet-Higgins, *J.*, 1949, 971.

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moistened with concentrated sulphuric acid to remove ammonia and finally through another 100 cm. column packed with potassium hydroxide pellets to remove any sulphuric acid and to dry the nitrogen, which was then passed through a glass trap packed with chemically clean glass wool, maintained in liquid nitrogen; this trap was near its point of use to minimise reintroduction of moisture. All preparations and manipulations were protected from air and moisture by means of this gas. Where possible direct incidence of strong light was also avoided.

Diethyl ether and dioxan were purified as described by Mackle and Ubbelohde [7] and Holmes-Walker and Ubbelohde.[3] Dimethoxyethane was stored over potassium hydroxide pellets for seven days, refluxed over sodium for 12 hr., and distilled at 81—82°.

Preparation of Sodium Addition Complexes.—A slurry of sodium–acridine complex in dioxan has been described.[8] Complexes between other benzoquinolines and sodium have not hitherto been reported.

Preparations in ethereal solution were preferred where possible, as the solvent is easily removed. Sodium–3 : 4-benzoquinoline and –7 : 8-benzoquinoline, were prepared by refluxing the heterocyclic compound in diethyl ether with sodium wire for 2—3 days.

5 : 6-Benzoquinoline reacted too slowly in diethyl ether, so dimethoxyethane was used. 2 : 3-Benzoquinoline in both dimethoxyethane and dioxan gave a characteristic green complex, but dioxan was used in definitive preparations because it gave bigger yields. The slurries were converted into solvent-free powders by methods similar to those previously described.[2,3]

Their conductance parameters and colours are recorded in Table 1.

So far as we know, limiting compositions of the complexes $(Na)_xArN$ were attained in preparations where sufficient reaction time was allowed, as recorded in Table 1.

A much more rapid method of preparation (cf. Part IV), by use of ultrasonic activation of the sodium, gave approximately the same limiting composition for the monosodium complex which appears to refer to an equilibrium between the benzoquinoline in ether and solid sodium on one side and the monosodium complex as a solid in contact with ether on the other at the boiling point of diethyl ether.

Further enrichment of the solvent-free solids was achieved as previously described [2,3] by warming them to about 100° in high vacuum. This led to sublimation of some unchanged 3 : 4-benzoquinoline (identified by mixed m. p.) and darkening. Thus $Na_{1\cdot1}$(3 : 4-benzoquinoline) is orange whereas $Na_{1\cdot49}$(3 : 4-benzoquinoline) is black. Vacuum sublimation gave no further enrichment of the sodium–acridine complex prepared in dioxan, [$Na_{1\cdot07}$(2 : 3-benzoquinoline)]. Enriched complexes are asterisked in Table 1.

All the complexes were spontaneously inflammable in air, and Na_x(7 : 8-benzoquinoline) occasionally decomposed explosively. Safety screens were used where appropriate.

Analysis. After trials of alternative methods the sodium complexes were analysed gravimetrically as follows: 0·1—0·5 g. of the addition compound was weighed under nitrogen and dissolved in 50 ml. of N-hydrogen chloride in approximately 95% ethyl alcohol. This solution was then evaporated to dryness and baked under two 250w infrared lamps. A few ml. of distilled water were added to the solids, and the insoluble organic product was filtered off from the aqueous sodium chloride solution, which was then dried and baked to constant weight with the infrared lamps. The sodium content was calculated from the weight of pure sodium chloride so obtained. As a check, the water-insoluble organic portion was dried and weighed; its total mass corresponded in all cases examined with the sodium analysis. The success of this method of analysis depended in part upon the fact that the organic products of decomposition of 3 : 4-, 5 : 6-, and 7 : 8-benzoquinoline complexes were practically insoluble in water. Under comparable conditions the 2 : 3-isomer gave an organic product readily soluble in water; in this case, after the solution obtained on decomposition had been evaporated to dryness, the white organic product was cautiously burned away with a Bunsen flame, which left the sodium chloride unchanged.

From sodium–acridine the organic decomposition product was apparently dihydroacridine, and was slightly soluble in dilute hydrochloric acid. The brown or black decomposition products from the other sodium complexes were insoluble in water, diethyl ether, or benzene, and melted between 200° and 300°. Possibly dimers (V) are obtained, though these could be formed at the moment of exchange of a proton for the sodium.

[7] Mackle and Ubbelohde, *J.*, 1948, 1161.
[8] Schlenk and Bergmann, *Annalen*, 1928, **463**, 281.

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Addition Complexes with Bromine.—Originally, complexes were precipitated from carbon tetrachloride solution by addition of bromine.[4] A more convenient and flexible route was direct addition of bromine from the vapour. For this purpose the appropriate heterocyclic substance was contained as a thin layer at the bottom of a weighed glass vessel provided with a standard ground stopper. A set of such containers were left open inside a desiccator together with a dish of bromine, and were closed and removed after various periods. Excess of bromine vapour was then removed from above the solid in any container, by blowing nitrogen for 5 min. over it, and the open container was finally kept for several hours over potassium hydroxide pellets in a vacuum desiccator to permit equilibration in the solid by diffusion. It was then weighed. At room temperature any loss of bromine from the solids proceeded only very slowly. For example, $(Br_2)_{1\cdot41}$(3 : 4-benzoquinoline) changed to $(Br_2)_{1\cdot40}$(3 : 4-benzoquinoline) during 18 hours' storage over potassium hydroxide in a partially evacuated desiccator.

On being warmed in a vacuum of about 10^{-3} mm. Hg to just below the m. p. (*ca.* 100°), any complex lost bromine more rapidly. Over 95% of the bromine could be recovered quantitatively in a liquid-nitrogen trap in a few hours, thus verifying that no permanent substitution had occurred in the heterocyclic nucleus. Complete removal of bromine from $(Br_2)_{1\cdot40}$(3 : 4-benzoquinoline) in this way yielded 3 : 4-benzoquinoline. Heating of the solids for shorter periods in this way led to intermediate compositions, which gave a convenient alternative approach from the bromine-rich end for some of the compositions required.

Analysis. When the bromine addition complexes were formed from the solid heterocyclic compounds, compositions were determined by direct weighing. The complex precipitated on adding bromine in carbon tetrachloride to acridine in carbon tetrachloride [4] was isolated, washed, and analysed by dissolving it in warm ethyl alcohol and estimating the bromine with potassium iodide and sodium thiosulphate. Considerable oxidation of the alcohol to acetaldehyde was observed. Similar oxidative properties were shown by the 1 : 1 bromine adducts [Br_2(benzoquinoline)] of the other benzoquinolines or when the bromine content exceeded this composition; it was verified that up to 90% of the bromine present oxidised ethyl alcohol to acetaldehyde, at least for $y \geqslant 2$ in $(Br_2)_y$(benzoquinoline).

Specific Volumes of the Complexes.—The object was to evaluate the excess volume $V_1 - V_2 = V_{ex.}$ where V_1 is the volume occupied by one formula weight of the complex X_n(benzoquinoline), and V_2 is the sum of the volumes occupied by one formula weight of the aromatic molecule and n formula weights of the electron donor or acceptor X.

Excess volume is plotted as a function of y for bromine complexes in Fig. 1. For $Na_{1\cdot07}$(2 : 3-benzoquinoline) the excess volume was found to be −30·4 c.c. per g.-atom of sodium.

All densities were measured at 20°. The low m. p.s of the complexes of bromine with 7 : 8-benzoquinoline (they are viscous liquids at room temperature) made it necessary to melt these into the pycnometer. Results are recorded in Fig. 1.

Electrical Conductances of the Solids.—Electrical conductivities of the complexes were measured in a valve-voltmeter circuit. *H* was the live terminal, and *I* the neutral.

The clean, dry cell (Fig. 2) was flamed with a soft Bunsen flame and evacuated. After about 15 min. pure nitrogen was allowed to fill the cell through *F*. Thereafter a constant stream of nitrogen was maintained throughout the measurements. Sufficient powder was introduced from a sample tube, fitted with an adaptor through *A*, to pack a column a few mm. long between copper electrodes *B* and *C* fitted with platinum caps. The upper electrode joined to the end of a brass stem was then carefully lowered on the powder and a rubber sleeve *D* was slipped on the main arm of the cell. A small glass tube *G* passing through this sleeve helped to keep the stem vertical; it formed the outlet for the nitrogen stream, and reduced it to the minimum necessary for protection of the sample. Finally, cylindrical lead weights were placed on the platform *E* fused to the stem, and the length of the sample column was measured with the aid of a lens and small steel scale. Pressures applied in this cell were 8—12 kg./cm.^{2}. Within this range the conductances were not appreciably affected by pressure and the results were reproducible in a temperature cycle.

The filled cell was placed in a liquid-paraffin bath maintained to $\pm 0\cdot5°$ over a range of about 30°. Resistances of the sample were measured so as to calculate the specific conductivity. The use of a valve voltmeter [3] calibrated with standard resistances up to 10^{10} ohms permitted measurements of column resistance with current densities as low as 5×10^{-10} A/cm.^{2} and with voltage gradients as low as 2 v/cm.

As previously described,[2] specific conductances, σ, were obtained by calculation from

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smoothed linear plots of resistance against column length for sodium–acridine (with $n = 1{\cdot}07$); these plots passed through zero, showing that electrode effects could be neglected. For the other complexes a single column length was used, and electrode effects were neglected in

FIG. 1. *Excess molar volume as a function of molar proportion of bromine in the benzoquinoline complex. (For* I, II, III, IV, *see formulae, p.* 983.)

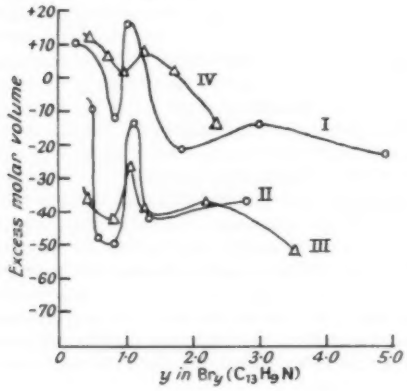
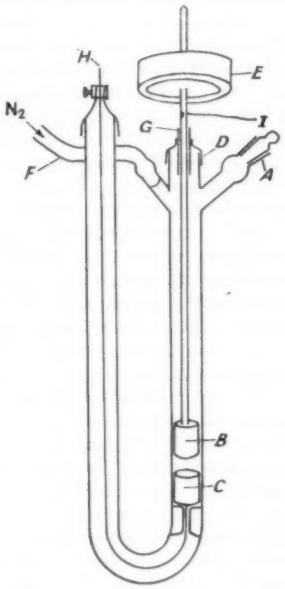


FIG. 2. *Conductivity cell.*



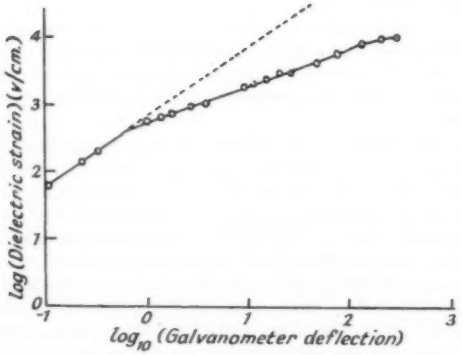


FIG. 3. *Non-ohmic characteristic of* $Na_{2\cdot01}$(7 : 8-*benzoquinoline*).

Broken curve corresponds to linear ohmic behaviour.

calculating σ. In the case of $Na_{2\cdot01}$(7 : 8-benzoquinoline), resistances were also measured at higher dielectric strains, up to 7500 v/cm. at up to 1×10^{-3} a/cm.^{2}. For this purpose a conventional sensitive D.C. galvanometer was used with a high-tension supply. Fig. 3 is a plot of dielectric strain against current. Conductance at these higher current densities is non-ohmic. Plots of log σ against $1/T$ (not shown) were in all cases linear within experimental error. Conductance results can thus be compactly recorded as in Table 1 on the basis of the equation

$$\log \sigma = \log \sigma_0 - E/kT$$

To test how far chance access of oxygen might alter the results, some samples of the complexes were deliberately exposed to air before making resistance measurements. The general

effect was that complexes such as $Na_{2\cdot01}$(benzoquinoline) showed marked increase of electrical conductance. Complexes such as Br_2(benzoquinoline) remained practically unaltered.

TABLE 1. *Conductivity parameters of benzoquinoline complexes.*

	Sodium complexes						Bromine complexes					
Isomer	Prepn. or solvent *	x *	Colour †	$\log_{10}\sigma_{293}$ (ohm^{-1} cm.$^{-1}$)	E (ev)	$\log_{10}\sigma_0$ (ohm^{-1} cm.$^{-1}$)	Prepn. or solvent	y	$\log_{10}\sigma_{293}$ (ohm^{-1} cm.$^{-1}$)	E (ev)	$\log_{10}\sigma_0$ (ohm^{-1} cm.$^{-1}$)
2 : 3	C	0	y	−18·25	2·52	24·955	+B	0·23	−15·020	2·39	25·880
,,	D	1·07	g	−15·74	1·99	18·375	+B	4·90	−15·420	2·09	20·380
3 : 4	E	1·11	o-br	−21·61	2·34	18·515	+B	0·49	−10·250	0·75	2·600
3 : 4	E	1·26	d-br	−12·65	1·49	12·90	−B	1·19	−6·893	0·45	0·822
3 : 4	E	1·49	b	−9·88	0·35	−3·88	−B	1·89	−6·750	1·57	22·830
3 : 4	—	—	—	—	—	—	−B	2·43	−6·323	0·50	2·260
3 : 4	—	—	—	—	—	—	+B	2·81	−5·607	0·37	0·710
5 : 6	M	1·60	d-v	−12·86	1·18	7·38	+B	3·39	−7·500	0·85	7·009
7 : 8	E	1·10	o-br	−18·38	2·15	16·49	+B	1·92	−6·125	1·49	19·430
7 : 8	E	2·01	b	−13·50	1·11	5·53	—	—	—	—	—
7 : 8	E	2·09	b	−10·07	1·00	7·07	—	—	—	—	—

* C, Chromatography; D, dioxan; E, diethyl ether; M, dimethoxyethane; +B, addition of bromine vapour; −B, removal of bromine vapour.

† b, Black; g, green; br, brown; o, orange; v, violet; y, pale yellow; d, dark.

DISCUSSION

In Part III,[9] the charge-transfer bonds between the benzoquinolines and the bromine were examined in solution. From the positions of the absorption bands, there was evidence that the sequence of increasing electron-donor properties follows the order 3 : 4-benzoquinoline < 5 : 6-benzoquinoline < 7 : 8-benzoquinoline < 2 : 3-benzoquinoline.

When solids of composition corresponding to the complexes previously examined in solution are studied, there are obvious possibilities of further polarisation interactions with nearest neighbours. Any electron-transfer processes that apply for a complex such $Na_x(C_{13}H_9N)$ or $(Br_2)_y(C_{13}H_9N)$ in isolation will obviously be profoundly modified when the nearest neighbours in the solid all have the same electronic affinity. Possibilities for switching electrons from one site to another in a solid solution of sodium or bromine with an aromatic molecule almost certainly account for the marked increase in electrical conductivity over that of the parent aromatic substance. The model previously suggested for such solid solutions [2,3] is that " quasi-metallic " bonds form between an acceptor or donor and the aromatic molecules packed in contract with it in the crystal. When these heterocyclic molecules function as acceptors with sodium the behaviour is similar to that of the homocyclic molecules previously studied.[2,3] There is a systematic trend of electronic properties as the proportion of sodium rises. Even quite small proportions of sodium markedly increase the conductance of the solid. As this proportion rises, the conductance rises, the activation energy for conductance falls (Fig. 4), and various other properties such as the deepening colour suggest increasing delocalisation of electrons in these solid complexes. In one case, sodium–acridine, marked electrostriction occurs on forming the complex, just as in the homocyclic complexes with anthracene. Thus the measured molecular volume of $Na_{1\cdot07}(C_{13}H_9N)$ is 154·7 c.c. and the calculated molecular volume of $C_{13}H_9N$ and 1·07Na is 187·2 c.c. Hence the excess volume = −32·5 c.c. or −30·4 per g.-atom of sodium. This corresponds to an almost completely ionic bond, the theoretical, calculated molecular volume for $Na^+_{1\cdot07}(C_{13}H_9N^-)$ being 164·1 + Δ c.c., where Δ is a small term to allow for the increase in volume for the formation of a negative ion: $C_{13}H_9N \longrightarrow C_{13}H_9N^-$.

When the heterocyclic molecules act as donors, polarisation bonding is more complex, possibly because of the dual rôle of the nitrogen atom and of the aromatic fused rings. Effects of progressive addition of bromine can be studied from the excess volume changes (Fig. 1) and from the conductance parameters. A tentative interpretation is that a dimeric

[9] Slough and Ubbelohde, *J.*, 1957, 911.

bromide (V) is first formed, as previously claimed to occur in concentrated slurries of sodium–acridine.[4] This leads to a break at the composition $Br(C_{13}H_9N)$; further addition of bromine leads to progressive loading of the system with more charge-transfer bonds and quite high total proportions of bromine can be held in this way.

An alternative view is that the first step on adding bromine is to form an *N*-bromoquinolinium bromide[4] of the composition (VI); subsequent bromine molecules then add at the various aromatic rings in the benzoquinoline molecule. Though this possibility cannot be excluded, at present there seems less evidence for it (cf. Part III[9]). There is also some evidence to suggest that the *N*-bromoquinolinium bromide does not form until a composition of $Br_2(C_{13}H_9N)$ is approached (cf. Fig. 4).

It is of obvious interest to determine how far the properties measured for these solids can be quantitatively related with the aromaticity of the molecules as measured in other ways. One significant property refers to the maximum number of donor or acceptor groups that can be held per heterocyclic molecule when the complex is allowed to reach

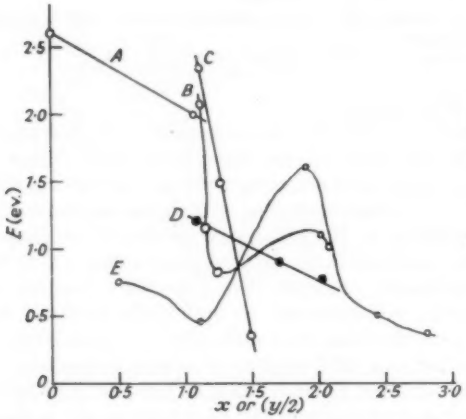


FIG. 4. *Activation energy E as a function of molar proportion of sodium or bromine in benzoquinoline complexes.*

A, Na(2:3-benzoquinoline); *B*, Na(7:8-benzoquinoline); *C*, Na(3:4-benzoquinoline); *D*, Na(anthracenes); *E*, $(Br_2)_y$(benzoquinolines).

equilibrium with free sodium or bromine, since this maximum gives some guide to a steep change in the strength of polarisation bonds as more donor or acceptor molecules are taken up. Though values are only approximate these maxima are at the following values of x: 7:8-, 2·09; 5:6-, 1·60; 3:4-, 1·49; 2:3-benzoquinoline, 1·07; and of y: 2:3-, 4·90; 3:4-, 3·80; and 5:6-benzoquinoline, 3·50. Br_n(7:8-benzoquinoline) forms liquids at the maximum uptake of bromine. Full interpretation of the interesting trends observed in the conductance parameters and in the molar volumes of the complexes must await a determination of structures, *e.g.*, by *X*-ray methods. Attention may be drawn to the steep changes of these parameters for certain complexes as the proportion of donor or acceptor increases. For example in the sodium complexes with 3:4- and 7:8-benzoquinoline the addition of alkali metal up to the composition $Na(C_{13}H_7N)$ appears to yield complexes with considerably lower electron energy levels than beyond this composition since the activation energy, E, for shifting an electron from the ground state of the complex to the conduction band shows a steep decrease near this composition. This parallels findings previously reported[3] for the compositions $Na_{2\cdot08}$(anthracene) and $Na_{2\cdot12}$(anthracene).

Owing to difficulties in varying the proportion of sodium in a solid complex, it is inconvenient to follow relationships between E and x in more detail for sodium complexes.

For the bromine complexes, marked variations in the excess molar volume with composition point to more than one type of bond formation, as previously stated.

Other Characteristics of the Electronic Conductance of the Solid Complexes.—For both

acceptor and donor complexes the usual correlation is found between small values of E and small values of log σ_0. This probably arises from a decrease in mobility as the number of conductance electrons rises. Numerical calculations on the basis of a model suggested by Mauy, Harnik, and Gerlich [10] use the equation $\sigma = en\mu$, where μ is the electron mobility (cm.^{2} volt^{-1} sec.$^{-1}$) and $n = N_0 \exp(-E/kT)$ where N_0, the effective density of states in the conducting levels of the crystal, is assumed to be 10^{21}.

Such calculations, not reproduced, again show that high mobilities are associated with high activation energies. This can be understood if the mean free path of the conduction electrons in these solids is determined by the average distance between activated sites, which also act as electron traps and become more numerous as E falls.

The non-ohmic conductance (Fig. 3), examined in detail for $Na_{2\cdot01}$(7 : 8-benzoquinoline), is found to be reversible in the sense that if the same sample is tested again at a lower voltage gradient, the original lower conductance reappears. It is presumed that if the voltage gradient is at all large, the dielectric strain on the polarisation bond increases the proportion of conduction electrons. The activation energy of such electrically strained samples is found to decrease, in accordance with this view.

A somewhat analogous model has been suggested for pure aromatic hydrocarbons.[11] The trend of the curve in Fig. 3 suggests that progressive electrical breakdown of the solid occurs as the strain increases.

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[10] Mauy, Harnik, and Gerlich, *J. Chem. Phys.*, 1955, **23**, 1733.
[11] Northrop and Simpson, *Proc. Roy. Soc.*, 1956, *A*, **234**, 124.

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192. *The Action of Bromine–Sulphuric Acid Mixtures on Methyl α-D-Glucopyranoside.*

By A. B. Foster and S. V. Vardheim.

Methyl α-D-glucopyranoside is hydrolysed on dissolution in bromine–sulphuric acid. Some of the liberated D-glucose is oxidised to D-gluconic acid but the major part undergoes reversion (polymerisation) and sulphation. Omission of the bromine leads to extensive decomposition of the carbohydrate.

Use of bromine–sulphuric acid for oxidative hydrolysis of barium hydrogen heparinate, barium chondroitin sulphate, and sodium mucoitin sulphate has been described by Wolfrom *et al.*[1] From barium hydrogen heparinate, monopotassium D-glucarate (saccharate), derived from the uronic acid moiety, was isolated whereas normal acidic hydrolysis led to total destruction of the released D-glucuronic acid.[2] Wolfrom and Rice [1] reasoned that, in the presence of bromine, the released D-glucuronic acid would be oxidised and hence stabilised. As first step in a study of the general applicability of the bromine–sulphuric acid reagent we have examined its action on methyl α-D-glucopyranoside.

Methyl α-D-glucopyranoside dissolved in 27N-sulphuric acid saturated with bromine did not char during several days at room temperature; omission of the bromine resulted in charring after *ca.* 5 hr. It is not known why charring should be retarded or inhibited by the presence of bromine. Increase in the sulphuric acid concentration above 27N caused rapid charring and decrease below 27N retarded the reactions to be described. The changes in optical rotation attending the dissolution of D-glucose, methyl α-D-glucopyranoside, and D-gluconic acid are shown in Fig. 1. Other information was obtained by

[1] Wolfrom and Rice, *J. Amer. Chem. Soc.*, 1946, **68**, 532; 1947, **69**, 1833.; Wolfrom and Brock Neely, *ibid.*, 1953, **75**, 2778.
[2] Foster and Huggard, *Adv. Carbohydrate Chem.*, 1955, **10**, 335.

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determination of reducing power of the mixture as a function of time. The appearance and disappearance, respectively, of reducing power when methyl α-D-glucopyranoside and D-glucose were dissolved in bromine–sulphuric acid are represented in Fig. 2. (curves *A* and *B*). If the reducing material was hydrolysed by acid then an increase in reducing power occurred (Fig. 2; curves *C* and *D* which are related to curves *A* and *B*, respectively).

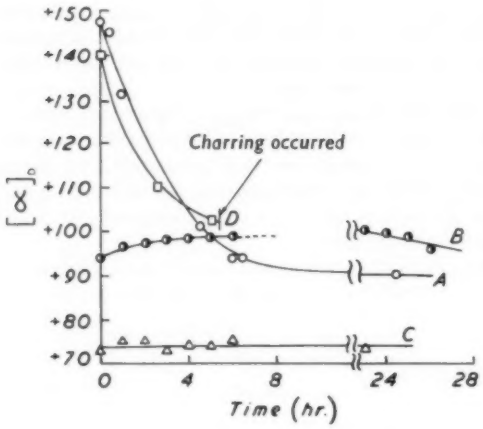

FIG. 1. *Changes in optical rotation (degrees) on the dissolution of derivatives of* D-*glucose in bromine–sulphuric acid.*

A, Methyl α-D-*glucopyranoside.*
B, D-*Glucose.*
C, D-*Gluconic acid.*
D, Methyl α-D-*glucopyranoside in the bromine-free reagent.*

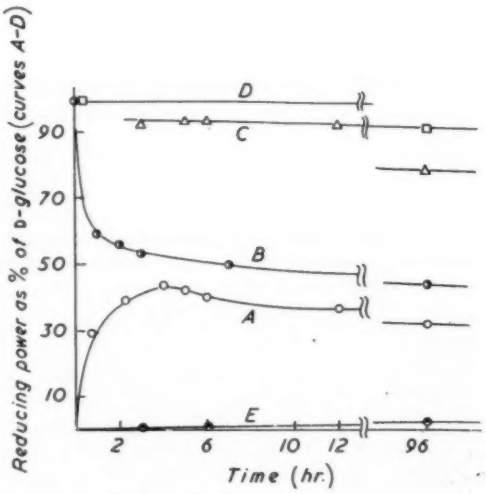

FIG. 2. *Reducing power of solutions of* D-*glucose and methyl* α-D-*glucopyranoside in bromine–sulphuric acid.*

Methyl α-D-*glucopyranoside:*
A, Reducing power of the diluted reaction mixture.
C, Reducing power after hydrolysis of the reducing substances in the diluted reaction solution.
E, Formation of D-*gluconic acid in the mixture.*

D-*Glucose:*
B as A.
D as C.

Paper ionophoretic examination [3] of the mixture after 24 hr. and after hydrolysis revealed a single reducing component with an M_G value [3] identical to that of D-glucose, and 1 : 2 : 3 : 4 : 6-penta-*O*-acetyl-β-D-glucose was subsequently isolated in 69% yield. This result indicates that little D-gluconic acid was produced and this was confirmed by ionophoretic separation of the D-gluconic acid and its determination by reaction with periodate. After 96 hr. only 6% of the methyl α-D-glucopyranoside had been converted into D-gluconic acid (Fig. 2; curve *E*). It is of interest that, after the reaction of barium hydrogen heparinate with bromine–27N-sulphuric acid [1] at 0° for 7 days, 64% of monopotassium

[3] Foster, *Chem. and Ind.*, 1952, 1050; Foster, Newton-Hearn, and Stacey, *J.*, 1956, **30**, and references cited therein.

D-glucarate and 59% of 2-amino-2-deoxy-D-gluconic acid (D-glucosaminic acid) could be isolated. The extent of oxidation here is clearly much greater than in the methyl α-D-glucopyranoside reaction.

Other experiments gave some indication of the fate of the D-glucose following its hydrolytic release from methyl α-D-glucopyranoside in bromine–sulphuric acid. A small amount of non-dialysable, and presumably polymeric, material could be isolated which gave D-glucose on total acidic hydrolysis, and traces of a series of oligosaccharides on graded acidic hydrolysis similar to that obtainable from dextran. Infrared analysis indicated that α-1 : 6-links might be present but other properties of the non-dialysable material suggested that it was not a simple poly-D-glucose. It is of interest that acid reversion of D-glucose yields a number of disaccharides in which *iso*maltose (α-1 : 6-link) and gentiobiose (β-1 : 6-link) predominate.[4]

Paper ionophoresis [3] of the mixture after 24 hr. revealed neutral substances and sulphates. The presence of ester sulphate corresponding to 85% of D-glucose monosulphate was determined by hydrolysis of the diluted mixture. Attempts to fractionate the products on charcoal–Celite [5] were only partially successful. A mixture of D-glucose and D-glucose monosulphate (as revealed by paper ionophoresis) was readily eluted from the column with water and had reducing power equivalent to 25% of the theoretical maximum D-glucose content of the mixture and contained ester sulphate corresponding to 18% of D-glucose monosulphate calculated on the same basis. Much material clearly had been retained by the column but application of an alcohol–water gradient elution [6] displaced a negligible amount of material. This result is surprising since it is known that anionic substances are released more readily from charcoal–Celite than are neutral substances [7] and large amounts of the material absorbed by the column must be sulphated.

After 24 hr. the mixture contained a little ether-soluble material with maximal light absorption (in the mixture) at 245 mμ. It is well known [8] that carbohydrates are dehydrated in strong solutions of sulphuric acid to yield ultraviolet-absorbing substances. The formation of this material together with the production of D-gluconic acid appears to account for the slow disappearance of D-glucose from the mixture (Curve *C*, Fig. 2).

Unlike its action on barium hydrogen heparinate, bromine–sulphuric acid therefore does not cause extensive oxidation of the reducing sugar which had been hydrolytically released from methyl α-D-glucopyranoside but brings about polymerisation (reversion) and/or sulphation.

Solutions of methyl α-D-glucopyranoside in bromine–sulphuric acid did not char during 5 hr. at 64° but an apparently different reaction pattern appeared to be operating (see Experimental).

Experimental

All operations were carried out at room temperature unless otherwise stated.

Action of Bromine–27N-Sulphuric Acid on Methyl α-D-Glucopyranoside.—The following mixtures were used: *A*, methyl α-D-glucopyranoside (1·0 g.) plus bromine-saturated 27N-sulphuric acid (25 ml.); *B*, the glycoside (3·0 g.) plus the acid reagent (25 ml.); *C*, the glycoside (2·5 g.) plus the acid reagent (75 ml.). In each case the glycoside was added to the acid reagent; it dissolved within a few minutes.

(a) *Optical activity of the solution.* The change in the optical activity of mixture *A* is shown in curve *A* of Fig. 1 ($[\alpha]_D$ calc. as methyl α-D-glucopyranoside). D-Glucose and D-gluconic acid similarly gave curves *B* and *C* (Fig. 1). Dissolution of methyl α-D-glucopyranoside in 27N-sulphuric acid gave curve *D* (Fig. 1); charring occurred after *ca.* 5 hr.

(b) *Determination of the reducing power.* Aliquot portions were withdrawn from mixture *A* and freed from bromine by aeration. A portion (3 ml.) was diluted with water (45 ml.),

[4] Thompson, Anno, Wolfrom, and Inatome, *J. Amer. Chem. Soc.*, 1954, **76**, 1309.
[5] Whistler and Durso, *ibid.*, 1950, **72**, 677.
[6] Lindberg and Wickberg, *Acta Chem. Scand.*, 1954, **8**, 569.
[7] Barker, Bourne, and Theander, *J.*, 1955, 4276.
[8] Rice and Fishbein, *J. Amer. Chem. Soc.*, 1956, **78**, 1005.

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neutralised (phenolphthalein) by titration with 2N-sodium hydroxide, and made up to 100 ml. The reducing power of this solution was determined by Shaffer and Hartmann's method;[9] curve *A* of Fig. 2 was obtained in this way. Determination of the reducing power of D-glucose was not affected by the presence of excess of sodium sulphate or sodium bromide. Curve *B* (Fig. 2) was similarly obtained for D-glucose.

In separate experiments aliquot portions were withdrawn from mixture *A* and aerated, and a portion (3 ml.) diluted with water (45 ml.). The solution was heated on a boiling-water bath for 3 hr., and then neutralised, and the reducing power determined as described above. Curve *C* (Fig. 2) was thus obtained and similarly curve *D* for D-glucose.

Paper ionophoresis of the diluted and neutralised solutions [the apparatus and technique previously described being used [3] with borate (pH 10) and glycine (pH 11) buffers and development with aniline hydrogen phthalate [10]] indicated the presence of neutral carbohydrates (including D-glucose) and anionic substances (sulphates) before hydrolysis and D-glucose after hydrolysis. Similar results were obtained with mixture *A* after it had been stored at 0°.

Mixture *B* was put aside for 24 hr., then diluted, aerated, and neutralised. The solution was concentrated, freed from precipitated sodium sulphate, concentrated (to *ca.* 10 ml.), made 2N with respect to sulphuric acid, and heated on a boiling-water bath for 3 hr. The residue obtained after neutralisation and concentration of the solution was acetylated (acetic anhydride and sodium acetate) and gave 1 : 2 : 3 : 4 : 6-penta-*O*-acetyl-β-D-glucose (4 g., 69%), m. p. 129—130°.

(c) *Determination of ester sulphate.* After 24 hr. a mixture *B* was diluted, aerated, and neutralised in the usual way. Free sulphate ion was removed by the addition of an excess of barium chloride, and the solution remaining was evaporated to dryness. The residue was boiled with nitric acid (3 : 2-concentrated nitric acid–water; 25 ml.) for 1 hr. and the barium sulphate (3·08 g., corresponding to 85% of D-glucose monosulphate) isolated in the usual way. Hydrolysis with 2N-hydrochloric acid at 95—100° for 3 hr. gave a similar yield (3·15 g.) of the barium sulphate confirming that curve *C* (Fig. 2) represents total release of reducing power.

(d) *Attempted fractionation of the mixture.* A mixture *B* after 24 hr. was diluted, aerated, neutralised, and concentrated (to *ca.* 25 ml.) at 25—30°(bath)/12—15 mm. Precipitated sodium sulphate was removed and the remaining solution, which contained only a small amount of free sulphate ions, was introduced on a charcoal–Celite column (5 × 50 cm.), and eluted with water. Unidentified material (maximal absorption at 257 mμ and 245 mμ) and sodium sulphate were eluted in the first 225 ml. The next 875 ml. was optically active and contained reducing power equivalent to 25% of the D-glucose theoretically derivable from the initial methyl α-D-glucopyranoside and ester sulphate corresponding to 18% of D-glucose monosulphate calculated on the same basis. Paper-ionophoretic examination in borate buffer (pH 10) and development with aniline hydrogen phthalate [10] revealed two reducing components with M_G values [3] identical with those of D-glucose and D-glucose 3-sulphate.

Further elution of the column with an ethanol–water gradient [6] up to 30% alcohol caused the release of negligible amounts of material.

(e) *Determination of the D-gluconic acid produced.* D-Gluconic acid is readily determined in 0·1—1·0 mg. amounts by reaction with periodate,[11] and a good recovery from Whatman No. 3 paper after ionophoresis in glycine buffer (pH 11) was obtained.

Mixture *A* (3 ml.) was diluted, aerated, neutralised, and made up to 25 ml. A portion (2 ml.) was introduced on to Whatman No. 3 paper (*ca.* 57 × 13 cm.) in a suitably located zone (*ca.* 8 × 1 cm.) (cf. Foster [3]) flanked by reference spots of D-gluconic acid. After ionophoresis in glycine buffer (pH 11) for 1·5 hr. under an applied potential of 1000 v the reference spots were located with the silver nitrate–sodium hydroxide reagents,[12] the D-gluconic acid zone from the reaction mixture eluted from the paper, and its content determined by titration with periodate. D-Gluconic acid formation is shown by curve *E* (Fig. 2).

(f) *Isolation of non-dialysable material.* After 24 hr. a mixture *B* was diluted, neutralised, and dialysed against running tap water for 5 days. When the solution was freeze-dried the non-dialysable material (0·115 g.; equivalent to *ca.* 4% of the potential D-glucose content of the mixture) was obtained as a hygroscopic powder, incompletely soluble in water. Hydrolysis

[9] Shaffer and Hartmann, *J. Biol. Chem.*, 1920, **45**, 365.
[10] Partridge, *Nature*, 1949, **164**, 443.
[11] Jackson, *Org. Reactions*, 1944, **2**, 341.
[12] Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444.

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with 2N-sulphuric acid for 3 hr. at 95—100° gave mainly D-glucose (detected chromatographically). Partial acidic hydrolysis (N-sulphuric acid; 1·75 hr. at 95—100°) followed by chromatography of the *N*-benzylglycosylamine derivatives [13] indicated traces of an oligosaccharide series similar to that obtained by the partial acidic hydrolysis of dextran. Infrared analysis (Nujol mull) of the non-dialysable material revealed peak absorptions at 1645(w), 971(s), 938(m), 920(m), 896(m), 872(s), 843(w), 800(w), and 767 cm.$^{-1}$ (m). The absorptions at 920, 843, and 767 cm.$^{-1}$ would be expected for a polyglucosan containing 1 : 6α-links.[14]

(g) *Development of ultraviolet absorption properties.* A mixture *C* after 24 hr. was aerated and a portion (3 ml.) withdrawn and diluted with water (97 ml.). This solution had maximal absorption at 245 mμ; exhaustive extraction with ether removed material (maximal absorption at 226 mμ) and left a weak residual absorption at 257 mμ.

In a separate experiment a mixture *A* was set aside at room temperature for 24 hr. and then heated at 65° for 5 hr. There was no charring but a tremendous increase occurred in the optical density at 245 mμ. The reducing power determined as in (b) was unchanged (20%) after hydrolysis.

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[13] Bayly and Bourne, *ibid.*, 1953, **171**, 385.
[14] Barker, Bourne, Stephens, and Whiffen, *J.*, 1954, 3468; Barker, Bourne, Stacey, and Whiffen, *J.*, 1954, 171.

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193. *The Antisymmetric Stretching Band of Carbodi-imides.*

By G. D. MEAKINS and R. J. MOSS.

The antisymmetric stretching vibrations of carbodi-imides give rise to exceptionally strong bands in the infrared spectrum. The intensities of these absorptions have been evaluated by several methods, and the relative merits of these methods are discussed.

THE infrared spectra of carbodi-imides R·N:C:N·R have received little attention beyond the brief statement by Khorana [1] that they have absorption bands near 2150 cm.$^{-1}$. A systematic investigation of several carbodi-imides, described here, showed that these compounds have characteristic peaks between 2150 and 2100 cm.$^{-1}$, a range which is reasonable by analogy with similar absorptions of many other groups containing a unit X=Y=Z with two double bonds joined to a common atom.[2]

Moreover, the carbodi-imide bands are extremely strong in a barren region of the spectrum, and thus provide a good opportunity for precise intensity measurements. The main purpose of the present work is therefore the use of the carbodi-imide spectra as a basis for comparing several methods of evaluating infrared intensities.

EXPERIMENTAL

*Preparations.—Di-*sec.*-butylcarbodi-imide.* Yellow mercuric oxide (25 g.) was added to a suspension of finely powdered *NN'*-di-*sec.*-butylthiourea (9 g.; m. p. 102—103°) in a mixture of dry carbon disulphide (150 c.c.), magnesium sulphate (30 g.), and sulphur (0·2 g.). The mixture was shaken for 2 hr., then filtered, and the insoluble material washed with carbon disulphide. Removal of solvent *in vacuo* from the combined filtrate and washings, and distillation of the residue afforded *di*-sec.*-butylcarbodi-imide* (6 g.), b. p. 68—68·5°/10 mm. (Found: C, 71·2; H, 11·75. $C_9H_{18}N_2$ requires C, 70·8; H, 11·7%).

*Di-*p*-methoxyphenylcarbodi-imide.* Yellow mercuric oxide (16 g.) was added in portions to a refluxing mixture of *NN'*-di-*p*-methoxyphenylthiourea (10 g.; m. p. 197—198°), acetone

[1] Khorana, *Chem. Rev.*, 1953, **53**, 145.
[2] See, *inter al.*, Herzberg, *Discuss. Faraday Soc.*, 1950, **9**, 92; Davison, *J.*, 1953, 3712.

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(400 c.c.), and sulphur (0·2 g.). After a further 20 minutes' boiling, the precipitate (largely mercuric sulphide) was collected and washed with acetone (100 c.c.). The bulk of the combined filtrates was reduced to 50 c.c., light petroleum (50 c.c., b. p. 60—80°) was added, and the mixture was cooled in ice. After removal of insoluble material the filtrate was evaporated to dryness, and the residue was twice crystallised from light petroleum to give *di*-p-*methoxyphenylcarbodi-imide* (6·4 g.), m. p. 49—50° (Found: C, 71·0; H, 5·5. $C_{15}H_{14}O_2N_2$ requires C, 70·9; H, 5·5%).

The remaining compounds were prepared by published methods (constants and references are given in the Table).

Spectroscopy.—The spectra were recorded over the 2300—2000 cm.$^{-1}$ region on a Perkin-Elmer double-beam spectrometer (sodium chloride prism) operating with source current 0·35 amp., slit programme 927, gain 7, response 2/2, scanning speed 15 cm.$^{-1}$/min., linear frequency scale 12·5 cm.$^{-1}$/cm. Each compound was examined in carbon tetrachloride solution in a 1 mm. cell at five concentrations. Errors in the concentration figures were minimised in the usual way (preparation of large volumes of solution, use of weighed amounts of solvent, precautions against evaporation losses).

Calculation of Intensities.—It is generally recognised that the area under an absorption band affords a more accurate measure of intensity than the apparent extinction coefficient. An authoritative treatment of this subject was given by Ramsay [3] in 1952, but only a few applications [4] of his methods have appeared since then. Four methods of treating area data were used with the carbodi-imide spectra, the procedure and terminology adopted being similar to Ramsay's.

The following definitions apply:

$$B \text{ (apparent integrated absorption intensity)} = \frac{1}{cl}\int \ln\left(\frac{T_0}{T}\right)_\nu . \, d\nu$$

where c = concentration of the solution in moles/l., l = path-length in cm., T_0 and T = apparent intensities of the incident and transmitted radiation when the spectrophotometer is set at frequency ν.

$$A \text{ (true integrated absorption intensity)} = \frac{1}{cl}\int \ln\left(\frac{I_0}{I}\right)_\nu . \, d\nu$$

where I_0 and I refer to monochromatic radiation.

$$\varepsilon^a \text{ (apparent molecular extinction coefficient)} = \frac{1}{cl}\log_{10}\left(\frac{T_0}{T}\right)_{\nu_m}$$

where ν_m = frequency of maximal absorption.

$$\text{Area } D = \int_{\nu_m - 40}^{\nu_m + 40} \ln\left(\frac{T_0}{T}\right)_\nu . \, d\nu \qquad \text{Area } E = \int_{\nu_m - 40}^{\nu_m + 40} \left(\frac{T_0 - T}{T}\right)_\nu . \, d\nu$$

$\Delta\nu_{\frac{1}{2}}^a$ and $\Delta\nu_{\frac{1}{2}}^t$ = apparent and true half-intensity band widths.

Two examples are shown to illustrate the detailed working by which the methods were applied.

Dibenzylcarbodi-imide (a).—Background absorption (solvent in both beams) = 2%. Effective slit width of spectrometer at ν_m (2140 cm.$^{-1}$) = 12·7 cm.$^{-1}$

Method 1 (*extrapolation*). The five experimental curves of frequency against percentage of absorption were replotted to give frequency (from 2180 to 2100 cm.$^{-1}$) against ln (T_0/T), and the areas under the curves (areas D) were measured with a planimeter. Wing corrections (obtained from Table V of Ramsay's paper [3]) were applied to the D values, and from the corrected figures values of B (apparent integrated absorption intensity) were calculated. A graph of B against ln $(T_0/T)\nu_m$ was plotted, and the best straight line was drawn such that the slope was $A\theta$ and the intercept (on the B axis) was A. (A is the true integrated absorption intensity: θ was found from Ramsay's Table IV.[3])

Method 2 (*proportional correction*). The wing corrections were taken as 10% of the D values.

[3] Ramsay, *J. Amer. Chem. Soc.*, 1952, **74**, 72.
[4] *E.g.*, Jones, Ramsay, Keir, and Dobriner, *ibid.*, p. 80; Bürer and Günthard, *Helv. Chim. Acta*, 1956, **39**, 356.

B values were calculated, and these were increased by 2% to give figures for *A*. The details were :

Concn. (mg./ml.)	Max. abs. (%)	Area *D* (cm.$^{-1}$)	$\Delta\nu_{\frac{1}{2}}^{e}$ (cm.$^{-1}$)	$\Delta\nu_{\frac{1}{2}}^{i}$ (cm.$^{-1}$)	ε^{e} (mole^{-1} l. cm.$^{-1}$)
1·1	77	45·4	25	19·8	1270
0·765	66	32·2	25	19·2	1330
0·626	59	26·5	25	19·1	1340
0·516	53	22·0	25	18·8	1370
0·322	38	13·8	25	18·7	1370

Method 1 (extrapolation)			Method 2 (proportional correction)		
Wing correction (%)	$10^{-4}B$ (mole^{-1} l. cm.$^{-2}$)	$10^{-4}A$	Wing correction (%)	$10^{-4}B$ (mole^{-1} l. cm.$^{-2}$)	$10^{-4}A$
18·3	10·8	11·35	10	10·1	10·3
17·6	11·0	($\theta = -0·033$)	10	10·3	10·5
17·5	11·0		10	10·3	10·5
17·7	11·1		10	10·4	10·6
17·1	11·2		10	10·5	10·7

Diisopropylcarbodi-imide (b).—Background absorption = 1%.

Method **3** (*variable correction*). The values of ln $(T_0/T)\nu_m$ were corrected (by using Ramsay's Table I [3]) to give ln $(I_0/I)\nu_m$ figures and hence ε^{i} values. Areas *E* were found by measuring the areas under the experimental curves of frequency (from 2168 to 2088 cm.$^{-1}$) against percentage of absorption. The *E* values were corrected for wing errors (Ramsay's Table VII). Figures of *A* were calculated from $A = (\phi \times \text{corrected } E/cl)$ (ϕ values from Ramsay's Table VI).

Method **4** (*no correction*). The intensity values were taken as D/cl. Details (units as above) were :

Concn.	Max. abs.	Area *D*	Area *E*	$\Delta\nu_{\frac{1}{2}}^{e}$	$\Delta\nu_{\frac{1}{2}}^{i}$	ε^{e}	ε^{i}
0·57	79	38·9	25·9	20	13·3	1490	2260
0·43	71	30·9	22·4	20	13·0	1560	2340
0·28	57	21·0	16·3	20	12·7	1630	2420
0·24	52	18·0	14·4	20	12·3	1630	2460
0·189	42	13·1	11·3	20	12·0	1550	2200

Method 3 (variable correction)		Method 4 (no correction)
Wing correction	$10^{-4}A$	Intensity
19·8	10·7	8·6
17·6	11·2	9·05
15·0	11·0	9·45
13·8	10·8	9·45
12·8	10·2	8·73

Discussion

The frequencies of maximal absorption for a series of carbodi-imides are shown in the Table. The single strong band between 2140 and 2125 cm.$^{-1}$ in each of the compounds (*a*—*f*) is clearly due to the antisymmetric stretching of the −N=C=N− system. Compounds (*g*), (*h*), and (*i*), which contain an aromatic group directly attached to the di-imide grouping, show two bands. These may arise by resonance coupling between the NCN fundamental and one of the aromatic overtones present in this region, the coupling enhancing the intensity of the normally weak aromatic band. Alternatively the effect may be due to conjugation of the di-imide system. No conjugated aliphatic compound was available for the present study, and a final choice between these and other possible explanations cannot be made.

The remainder of the Table shows apparent extinction coefficients and area data for the bands. The ε^{e} values and the *A* figures of methods 2, 3, and 4 are followed by error values. Since the object of any method of computation is to produce a constant value for the intensity of a band, the error values are expressed in a way that brings out the maximal deviation from the average values.

It is apparent that the di-imide bands are exceptionally strong, on both an extinction coefficient and an area basis (cf. carbonyl bands, which are normally regarded as very

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strong, having ε^a and A values of about 600 and 2·5 units respectively [4]). The errors in ε^a values depend markedly on the range in maximal absorption used. For example, in (*e*) the

Infrared frequencies for carbodi-imides, and average values (and errors) of intensities.

Units of intensities are as in detailed examples. Error figures, given in parentheses after average values, are maximum single errors, *i.e.*, the highest values of the difference between single values from 5 runs and the average, expressed as a percentage of the average value.

Carbodi-imide	ν_m (cm.$^{-1}$)	ε^a	*A* values: 1, Extrapoln.	2, Prop. corrn.	3, Variable corrn.	4, No corrn.
(*a*) Dibenzyl [5] (b. p. 144—145°/0·3 mm.)	2140	1340 (5·2)	11·35	10·5 (1·9)	10·9 (1·8)	9·37 (2·2)
(*b*) Di*iso*propyl [6] (b. p. 44—45°/13 mm.)	2128	1580 (5·7)	Imposs.	10·2 (5·4)	10·8 (4·8)	9·06 (5·1)
(*c*) Di-*sec*.-butyl [7]	2128	1540 (8·4)	11·1	10·4 (5·8)	11·3 (1·8)	9·3 (5·5)
(*d*) Di-*n*-butyl [6] (b. p. 88—89°/12 mm.)	2138	1560 (8·3)	Imposs.	9·13 (6·9)	10·9 (4·6)	8·14 (8·3)
(*e*) Diethyl [6] (b. p. 92—93°/260 mm.)	2138	1360 (11)	Imposs.	8·6 (6·8)	10·4 (4·3)	7·7 (8·0)
(*f*) Di*cyclo*hexyl [8] (b. p. 155—156°/10 mm.)	2130 *	1430 (—)	—	8·75 (—)	10·6 (—)	7·8 (—)
(*g*) Di-*p*-methoxyphenyl [7]	2142	1380 (2·9)	Not studied	16·0 (1·9)	Not applicable	14·3 (2·1)
	2120	1180 (3·4)				
(*h*) Di-α-naphthyl [9] (m. p. 90—91°)	2152	1680 (4·8)	Not studied	24·1 (2·5)	Not applicable	21·4 (2·3)
	2100	400 (5·5)				
(*i*) Di-*p*-tolyl [10] (m. p. 53—54°)	2145	1440 (3·5)	Not studied	19·0 (4·2)	Not applicable	17·0 (4·1)
	2120	1560 (2·6)				

* Three runs only.

Refs.: 5, Zetsche and Fredrich, *Ber.*, 1940, **73**, 1114. 6, Lecher, Parker, and Long, U.S.P. 2,479,498/1949; *Chem. Abs.*, 1950, **44**, 4027. 7, This paper. 8, Schmidt, Hitzler, and Lahde, *Ber.* 1938, **71**, 1933. 9, Rotter and Schandy, *Monatsh.*, 1931, **58**, 245. 10, Zetsche and Nerger, *Ber.*, 1940, **73**, 467.

range 38—92% leads to a high error, whereas in (*h*), with a small error, the range was 40—70%. Method 1 (extrapolation) is the least satisfactory of the area methods. For its application a plot of B against $\ln (T_0/T)\nu_m$ must be a reasonably straight line, a condition which did not apply in three of the five cases studied. Even with (*a*) and (*c*) the values obtained for A are too high, and this tendency may be inherent in the method when large B values are involved.

The other area methods are more accurate than extinction-coefficient measurements, although the improvement is surprisingly small for compound (*b*). The superiority is clearer when the experimental conditions are varied more radically. Thus, examination of di*cyclo*hexylcarbodi-imide (*f*) with a calcium fluoride prism gave $\varepsilon^a = 1890$ (cf. NaCl, 1430) and A (method II) = 9·25 (cf. NaCl, 8·75). Method 3 (variable correction) is the most satisfactory, as shown by the error values and also by the fact that the A values for different compounds are closer together than they are in methods 2 (proportional correction) and 4 (no correction). Of methods 2 and 4 the former gives slightly smaller errors and more correct A values.

It is unfortunate that the variable-correction procedure cannot be applied to overlapping bands such as occur in (*h*), (*i*), and (*j*). In these cases the proportional-correction method is still valid, although the choice of frequency limits for integration is arbitrary. The use of a range 40 cm.$^{-1}$ above the higher, to 40 cm.$^{-1}$ below the lower frequency band recommended by Jones *et al.*[4] gives remarkably good results in the present examples. Attempts to resolve the bands graphically and determine separate areas led to far greater deviations from mean values. The ε^a values suggest that the band primarily associated

with the stretching mode is at *ca.* 2145 cm.$^{-1}$, while the 2100 cm.$^{-1}$ component is the coupled vibration.

For general purposes the proportional-correction procedure is the most suitable, in that it has two advantages, *viz.*, ease of calculation and applicability to overlapping bands, over the more refined methods involving varying corrections.

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194. *Infrared Absorption of* 1 : 2-*Disubstituted* cis-*Ethylenic Centres.*

By H. B. HENBEST, G. D. MEAKINS, B. NICHOLLS, and R. A. L. WILSON.

The infrared spectra of further groups of compounds containing disubstituted *cis*-double bonds in different environments are reported, attention being concentrated on the olefinic C–H out-of-plane bending vibration.

IN a previous study [1] the absorption of disubstituted *cis*-ethylenic centres at different positions in the steroid nucleus was investigated. It was found that the olefinic C–H out-of-plane bending absorption (800—650 cm.$^{-1}$) was the most useful in establishing the presence of this grouping, and that the results could be correlated with the degree of strain in the unsaturated bonds. The work has now been extended by the examination of simple mono- and bi-cyclic systems (Table 1) and compounds (largely steroids) in which the *cis*-double bond is conjugated with C=C or C=O groups (Table 2).

Tables.—The spectra were recorded on a Perkin-Elmer model 21 double-beam spectrometer fitted with a sodium chloride prism. The experimental conditions were as previously described,[1] except that carbon disulphide solutions were used in all regions. Intensity values, given in parentheses after the C–H out-of-plane bending frequencies, are in mole^{-1} l. cm.$^{-1}$ units.

TABLE 1. *Infrared frequencies (cm.$^{-1}$) of mono- and bi-cyclic compounds containing disubstituted* cis-*double bonds.*

No.	Olefinic C–H stretching	C=C stretching	Olefinic C–H out-of-plane bending *			
1 *cyclo*Pentene	3045	1612	695 (70)			
2 *cyclo*Hexene	3020	1650	718 (70)			
cyclo*Hex*-2-*enyl compounds* (I)						
3 (I; R = OH)	3022	1689	1651	724 (115)		
4 (I; R = OAc)	3030	1688	1651	727 (80)		
5 (I; R = OMe)	3035	1688	1650	725 (65)	702 (60)	
6 (I; R = OEt)	3025	1683	1651	724 (75)		
7 (I; R = Br)	3028	1687	1641	731 (250)	723 (100)	
cyclo*Hex*-3-*enyl compounds* (II)						
8 (II; R = OH)	3030	1649		733 (50)		655 (105)
9 (II; R = OAc)	3025	1662		741 (45)		654 (85)
10 (II; R = OMe)	3020	1654		730 (50)		†
11 (II; R = OEt)	3020	1654		735 (40)		655 (80)
12 *cyclo*Hex-1-en-4-one (III)	3020	1651		731 (20)		660 (95)
bicyclo[2 : 2 : 1]*Hept*-5-*en*-2-*yl compounds* (IV)						
13 (IV; R = CO_2H)				705 (140)		
14 (IV; R = CO_2Me)	3070			705 (190)		
15 (IV; R = CH_2·OH)	3070		715 (170)		704 (70)	
16 (IV; R = OAc)	3075		718 (190)		710 (105)	
17 (IV; R = CH_2·OMe)	3065		716 (140)		704 (75)	

* Intensities in parentheses. † Absorption rising steeply at 650 cm.$^{-1}$.

[1] Henbest, Meakins, and Wood, *J.*, 1954, 800.

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TABLE 2. *Compounds containing conjugated* cis*-double bonds, and, in square brackets, reference compounds without* cis*-double bonds. Prominent bands in the* 900—650 cm.$^{-1}$ *region, probably associated with olefinic* C–H *out-of-plane bending.*

		>C=CH–		–CH=CH–	
	Type (V)				
18	3β-Acetoxycholesta-6 : 8-diene			720 (130)	
19	3β-Methoxy-11α-methylergosta-6 : 8 : 22-triene			720 (105)	
	Type (VI)				
20	*cyclo*Hex-2-enone		752 (50)		730 (100)
21	*trans*-Δ^{1}-Octahydro-9-methyl-3-oxonaphthalene			782 (150)	
22	Cholest-1-en-3-one *			778 (170)	
23	Cholest-2-en-1-one		808 (75)		793 (55)
24	5α-Hydroxycholest-3-en-2-one			775 (145)	
	Type (VII)				
25	Δ$^{1(11):9}$-Decahydro-1 : 12-dimethyl-6 : 7-*iso*propylidenedioxy-2-oxophenanthrene			776 (155)	
26	[Δ$^{1(11)}$-Dodecahydro-1 : 12-dimethyl-6 : 7-*iso*propylidenedioxy-2-oxophenanthrene]			—	
27	Cholesta-4 : 6-dien-3-one (R = H) *	876 (265)	773 (45)		753 (65)
28	[Cholest-4-en-3-one *]	867 (140)		—	
29	[Ergosta-4 : 7 : 22-trien-3-one]	868 (140)		—	
30	Cholesta-3 : 5-diene-7-one (R = H)	884 (140)	778 (90)		733 (40)
31	[Cholest-5-en-7-one]	861 (60)		—	
32	[3β-Acetoxycholest-5-en-7-one *]	869 (75)		—	
	Type (VIII)				
33	Cholesta-1 : 4 : 6-trien-3-one	892 (330)	765 (120)		695 (80)
34	Androsta-1 : 4 : 6-trien-3-one	892 (~350)	767 (115)		696 (75)
	Type (IX)				
35	Cholesta-1 : 3 : 5-trien-7-one	875 (220)	723 (215)		678 (215)

* Frequencies agree closely with those given by R. N. Jones *et al.*[4]

The C=O frequencies of some of these compounds are: no. 21, 1690; no 22, 1684; no. 23, 1682; no. 24, 1681; no. 35, 1661 cm.$^{-1}$.

Compounds: 9, 11, and 17, Henbest and Nicholls, unpublished work. 19, E. R. H. Jones, Meakins, and Stephenson, unpublished work. 35, Henbest and Wilson, *Chem. and Ind.*, 1956, 86. Compounds 21, 25, and 26, kindly supplied by Professor R. B. Woodward; no. 24 by Dr. W. Bergmann; nos. 33 and 34 by Dr. G. Rosenkranz and Dr. F. Sondheimer. The remainder were prepared by published methods.

In the *cyclo*hexene derivatives (I) and (II) the presence of substituents α or β to the double bond does not cause any marked change in the olefinic C–H stretching frequencies relatively to the value for *cyclo*hexene itself (3020 cm.$^{-1}$). The increase observed when comparing the *bicyclo*heptenes (IV) with *cyclo*pentene is probably associated with increased rigidity and/or strain in the *cis*-double bond in the bridged nucleus rather than with substitution at the β-position. Dissymmetry in the groups attached to the *cis*-double bonds increased in the sequence (IV)–(II)–(I), and this leads to clear distinctions between the three groups in the 1700—1600 cm.$^{-1}$ (C=C stretching) region. While no bands are observed for the *bicyclo*heptene derivatives, both *cyclo*hexene types give the expected (weak) 1650 cm.$^{-1}$ band, and the allylic systems (I) have a second (very weak) component near 1685 cm.$^{-1}$. A more marked case of unsymmetrical substitution leading to splitting of C=C absorption is found with vinyl ethers (CH_2=CH·OR), where a heteroatom is directly linked to the olefinic bond,[2] and in enol esters (unpublished observations).

cis-Double bonds in acyclic systems generally give one band associated with the olefinic C–H out-of-plane bending motion. But compounds with cyclic *cis*-bonds often give several bands which can be related equally to the olefinic centre, and it is not feasible to single out any particular component as the out-of-plane bending band.[1] In groups (I) and (IV) a change of substituent may cause a single peak to become a closely separated

[2] Meakins, *J.*, 1953, 4170.

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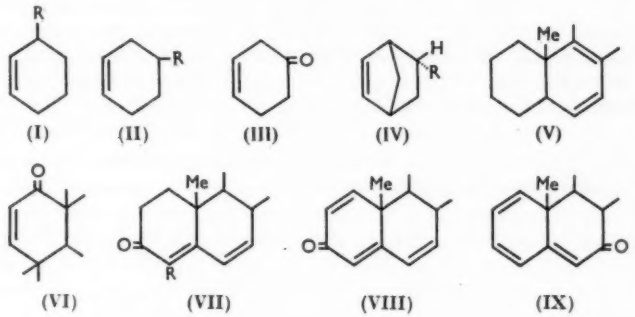
doublet, but despite this, general positions for the absorptions of systems (I), (II), and (IV) can be discerned. Group (I) has band(s) at ~725 cm.$^{-1}$ (ε 50—120). [3-Bromo*cyclo*hexene (no. 7) is exceptional in the intensity of its 731 cm.$^{-1}$ band. This effect is probably connected with the presence of halogen in a cyclic system : equatorial C–Br in bromosteroids and in bromo*cyclo*hexanes gives bands in the 750—700 cm.$^{-1}$ region.[3]] Compounds with β-substitution (II) have two bands, the weaker near 735 cm.$^{-1}$ and the stronger around 655 cm.$^{-1}$. The proximity of the latter to the end of the sodium chloride range introduces some uncertainty into the frequency and intensity figures : it also emphasises the fact that certain types of *cis*-bonds have at least some of their bending



bands below 650 cm.$^{-1}$ (cf. cholesta-3 : 5-diene discussed below). The increased intensities of the *bicyclo*heptene peaks are in line with our previous findings that increasing the degree of alkylation at the carbon atoms adjacent to a cyclic *cis*-bond enhances the intensity of absorption.

In a series of *cyclo*hexene derivatives the bending bands move to higher frequency as the strain of the system increases.[1] However, it appears that comparisons between *different* series cannot be made on this basis, since the more strained *cyclo*pentene and the *bicyclo*heptene compounds have frequencies (695 and ~710 cm.$^{-1}$) lower than that for the less strained *cyclo*hexene (718 cm.$^{-1}$).

Four of the conjugated compounds (nos. 22, 27, 28, and 32) shown in Table 2 have been studied previously by R. N. Jones and his collaborators in an important survey of the spectra of oxo-steroids.[4] They showed that a particular system (such as the $\Delta^{4:6}$-3-oxo-grouping) is asociated with a number of bands which persist unchanged throughout a series of steroids containing that system. To make specific assignments of these bands to different bonds and atoms within these systems is difficult : indeed, in complex cases, it may be impossible to make a satisfactory assignment in terms of localised vibrations. Nevertheless an attempt is made here to pick out certain peaks as being associated mainly with the *cis*-bond. It must be stressed that we do not imply that the bands shown in Table 2 are the only ones in which the C–H bending of the *cis*-bond is concerned, merely that they are the ones having a high " contribution " from the *cis*-bond.

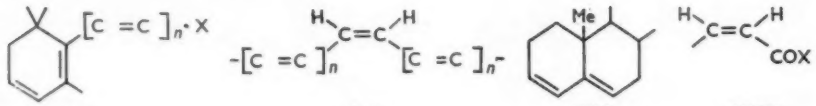
Previous knowledge of the effect of C=C conjugation on the *cis*-double bond frequencies is largely confined to polyenes. In type (X), where the *cis*-bond is part of a homoannular system, the out-of-plane bending frequency is relatively constant at ~725 cm.$^{-1}$ for a variety of end groups (X; R = CH_2·OH, COMe, CO_2Me, etc.).[5] The dienes of type (V) (nos. 18 and 19) with values of 720 cm.$^{-1}$ are in agreement with this. With acyclic *cis*-bonds (XI) the position of the band is more variable. The frequency appears to increase

[3] Barton, Page, and Shoppee, *J.*, 1956, 331.
[4] R. N. Jones, Herling, and Katzenellenbogen, *J. Amer. Chem. Soc.*, 1955, **77**, 651.
[5] Farrar, Hamlet, Henbest, and E. R. H. Jones, *J.*, 1952, 2657.

XUM

as conjugation is extended, reaching a value of ~780 cm.$^{-1}$ in cases such as 9 : 9′-*cis*-β-carotene.[6] (It should be noted that most of the " conjugating " double bonds in polyenes are trisubstituted : the same effects may not apply with other types of olefinic bonds; cf. the effect of conjugation with different types of double bonds on the bending frequency of *trans*-double bonds.[7, 8]) With the heteroannular cholesta-3 : 5-diene (XII) only weak bands occurred between 900 and 650 cm.$^{-1}$. Examination with a potassium bromide prism (kindly made by Dr. J. E. Page, of the Glaxo Laboratories) showed the main *cis*-band to be at 616 cm.$^{-1}$ (ε 150), the mono-olefin cholest-3-ene giving bands at 773 (ε 110) and 671 cm.$^{-1}$ (ε 125).

Conjugation of alicyclic *cis*-bonds with acid, ester, and amide groups [8] (XIII; X = OH, OR, NHR) moves the bending band from ~700 to 820 cm.$^{-1}$. From the spectra published by Schinz and his co-workers [9] it appears that this correlation is not applicable to conjugated ketones (XIII; X = alkyl). (It is difficult to find the bending bands in these cases; peaks around 750 cm.$^{-1}$ appear to be the most probable.) With the simplest cyclic example, *cyclo*hex-2-enone (no. 22) the main band appears at 730 cm.$^{-1}$, which represents a small increase with respect to *cyclo*hexene (718 cm.$^{-1}$), but in the more complex compounds (nos. 22—24), where the bi- or poly-cyclic skeleton reduces the flexibility of the *cyclo*hexenone ring, a larger increase occurs.



(X) (XI) (XII) (XIII)

The assignments shown for type (VII) are supported by comparisons between compounds containing a *cis*-bond and reference substances of similar structures (given in Table 2) lacking this function. In the remaining types, (VIII) and (IX), there are insufficient examples for general proposals. The main conclusion to be drawn is that conjugation of a cyclic *cis*-double bond with an oxo-group again moves the bending band(s) to higher frequency.

Compounds 27—35 all contain a >C=CH·CO− grouping which gives rise to strong peaks between 895 and 860 cm.$^{-1}$ attributable to the C−H bending band of the trisubstituted double bond, shifted from its normal position (~815 cm.$^{-1}$) by conjugation. The effect, which again involves frequency increase of an olefinic bending band by ketonic conjugation, has been noted previously for the Δ^4-3-oxo-system,[4,10] as has the fact that 3β-acetoxy-Δ^5-7-ketones absorb [4] near 904 and 867 cm.$^{-1}$. The absence of the higher-frequency band in the Δ^5-7-ketone (no. 31) indicates that this band is associated with the acetate group, and that of lower frequency with the olefinic bond.

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THE UNIVERSITY, MANCHESTER, 13. [*Received, October 8th,* 1956.]

[6] Oroshnik and Mebane, *J. Amer. Chem. Soc.*, 1954, **76**, 5719.
[7] Chapman and Taylor, *Nature*, 1954, **174**, 1011.
[8] Allan, Meakins, and Whiting, *J.*, 1955, 1874.
[9] Theus, Surber, Colombi, and Schinz, *Helv. Chim. Acta*, 1955, **38**, 239; Gamboni, Theus, and Schinz, *ibid.*, p. 255.
[10] Elks, *J.*, 1954, 468.

195. *The Reaction of Anthracene with Benzyl Radicals.*

By A. L. J. Beckwith and William A. Waters.

The thermal decomposition of di-*tert.*-butyl peroxide in toluene affords a convenient source of benzyl radicals. These react with anthracene at the *meso*-positions, giving 9 : 10-dibenzylanthracene (VII), 9 : 10-dibenzyl-9 : 10-dihydroanthracene (IV), 9 : 9 : 10-tribenzyl-9 : 10-dihydroanthracene (VI), and 10 : 10′-dibenzyl-9 : 9′ : 10 : 10′-tetrahydro-9 : 9′-dianthryl (II), all of which have been synthesised by independent routes.

Similar products have been isolated after reaction of benzyl chloride with the sodium and lithium adducts of anthracene.

Dehydrogenation of 9-benzyl- and 9 : 10-dibenzyl-9 : 10-dihydroanthracene by 2-cyano-2-propyl radicals, with mercaptoacetic acid as catalyst, has also been examined.

Cumyl radicals, produced from di-*tert.*-butyl peroxide in cumene, do not react with anthracene.

In a previous paper [1] we described the reactions of anthracene with the free radicals produced by thermal decomposition of di-*tert.*-butyl peroxide in chlorobenzene or *o*-dichlorobenzene. In these experiments the isolation of pure compounds was hindered by the presence in the crude reaction product of large amounts of resin, the formation of which was attributed to radical polymerisation initiated by the attack of methyl radicals upon the solvents. In order to study the behaviour of anthracene with a less reactive and more selective reagent we have now conducted the reaction with di-*tert.*-butyl peroxide in toluene and in cumene. In these solvents the resonance-stabilised benzyl and cumyl radicals are readily formed according to the following equations : [2]

$$Bu^tO{\cdot}OBu^t \longrightarrow 2Bu^tO{\cdot} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$Bu^tO{\cdot} \longrightarrow COMe_2 + Me{\cdot} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$PhMe + Bu^tO{\cdot} \longrightarrow Ph{\cdot}CH_2{\cdot} + Bu^tOH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$PhMe + Me{\cdot} \longrightarrow Ph{\cdot}CH_2{\cdot} + CH_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$PhPr^i + Bu^tO{\cdot} \longrightarrow Ph{\cdot}CMe_2{\cdot} + Bu^tOH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

$$PhPr^i + Me{\cdot} \longrightarrow Ph{\cdot}CMe_2{\cdot} + CH_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

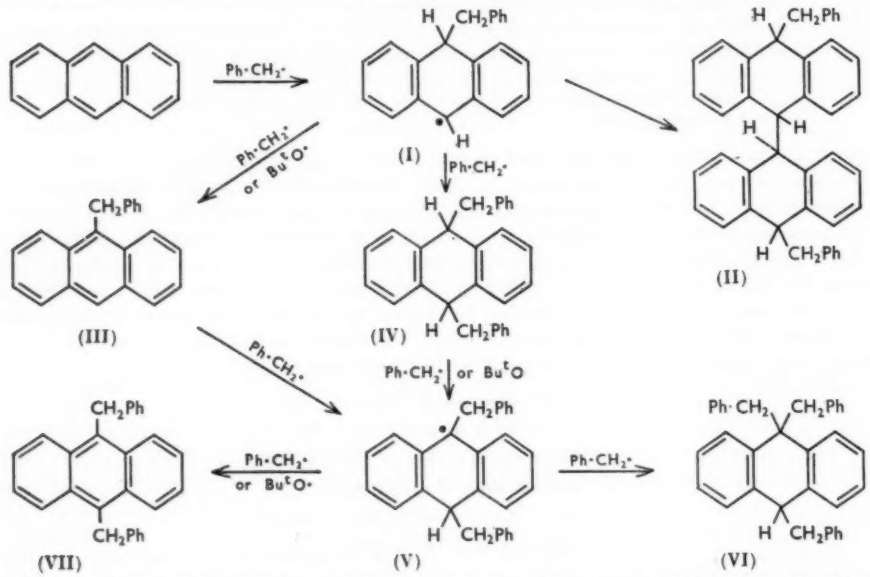
In cumene solution the cumyl radicals produced by reactions (5) and (6) dimerised to 2 : 3-dimethyl-2 : 3-diphenylbutane and the anthracene was not attacked. However, when the reaction was conducted in toluene solution with 1·7 moles of the peroxide per mole of anthracene all of the hydrocarbon was consumed and there were isolated 9 : 10-dibenzylanthracene (VII), 9 : 10-dibenzyl-9 : 10-dihydroanthracene (IV), 9 : 9 : 10-tribenzyl-9 : 10-dihydroanthracene (VI), and 10 : 10′-dibenzyl-9 : 9′ : 10 : 10′-tetrahydro-9 : 9′-dianthryl (II). Very little tar was formed in the reaction and the total yield of pure products was high.

The routes by which the various products were probably formed are indicated in the annexed scheme. Possibly the most interesting feature of the reaction is the simultaneous production of derivatives of both anthracene and 9 : 10-dihydroanthracene. This result supports the view that free-radical addition and substitution of aromatic compounds both proceed by the same initial step, *i.e.*, addition of a radical to a reactive carbon atom in the aromatic molecule. The fate of the radical so formed depends upon the nature of the reagent. With reactive radicals such as methyl the abstraction of hydrogen leads to substitution [1] but with the relatively stable 2-cyano-2-propyl radical only the addition compound is produced.[3]

[1] Beckwith and Waters, *J.*, 1956, 1108.
[2] Raley, Rust, and Vaughan, *J. Amer. Chem. Soc.*, 1948, **70**, 1336.
[3] Bickel and Kooyman, *Rec. Trav. chim.*, 1952, **71**, 1137.

XUM

The isolation of 9 : 9 : 10-tribenzyl-9 : 10-dihydroanthracene (VI) is of interest as there is no previous account of a trisubstituted compound formed by reaction of anthracene with free radicals although intermediates of this form have been supposed to occur in the oxidation of anthracene by lead tetra-acetate.[4] The diagram shows two ways by which this product (VI) might be formed. Of these, that involving addition of benzyl radicals to 9-benzylanthracene is the more probable for it is known that compounds such as 9 : 10-dibenzyl-9 : 10-dihydroanthracene (IV) are unexpectedly resistant to the abstraction of hydrogen by free radicals.[5] The fact that 9-benzylanthracene could not be isolated does not preclude its participation by this mechanism for it is known that 9-substituted anthracenes are more reactive than the parent compound towards attack by free radicals.[6]



The experiments of Rust, Raley, and Vaughan (*J. Amer. Chem. Soc.*, 1948, **70**, 1336) with di-*tert.*-butyl peroxide in cumene indicate that dehydrogenation by methyl radicals is unlikely to occur under our conditions.

Unlike Bickel and Kooyman [3] who observed both *cis*- and *trans*-addition of 2-cyano-2-propyl radicals to anthracene, we were able to isolate only one form of 9 : 10-dibenzyl-9 : 10-dihydroanthracene.

The structures of all the free-radical products have been confirmed by comparison with specimens synthesised by unequivocal methods. Thus 9 : 10-dibenzyl-9 : 10-dihydroanthracene (IV) was readily obtained by reduction of 9 : 10-dibenzylanthracene with sodium and pentyl alcohol,[7] and 9 : 9 : 10-tribenzyl-9 : 10-dihydro-10-hydroxyanthracene was similarly converted into 9 : 9 : 10-tribenzyl-9 : 10-dihydroanthracene (VI).

In view of the ready production of 9-benzylanthracene by treatment of anthrone with benzylmagnesium chloride it was expected that a similar reaction with dianthron-9-yl would lead to 10 : 10′-dibenzyl-9 : 9′-dianthryl. However, in this case the normal reaction was accompanied by fission of the bond joining the two anthracene nuclei and the only product was 9-benzylanthracene. 10 : 10′-Dibenzyl-9 : 9′-dianthryl was eventually

[4] Fieser and Putnam, *J. Amer. Chem. Soc.*, 1947, **69**, 1038.
[5] Kooyman and Strang, *Rec. Trav. chim.*, 1953, **72**, 342.
[6] Roitt and Waters, *J.*, 1952, 2695; Farenhorst and Kooyman, *Nature*, 1955, **175**, 598; Greenwood, *ibid.*, 1955, **176**, 1024.
[7] Bergmann and Fujise, *Annalen*, 1930, **480**, 188.

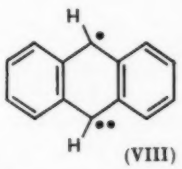
obtained by oxidation with ferric chloride of the Grignard reagent from 9-benzyl-10-bromoanthracene. The reduction of 10 : 10′-dibenzyl-9 : 9′-dianthryl with sodium in boiling pentyl alcohol resulted in fission of the molecule, and the only product was 9-benzyl-9 : 10-dihydroanthracene. When the reaction was repeated at a lower temperature in toluene solution the main product was 10 : 10′-dibenzyl-9 : 9′ : 10 : 10′-tetrahydro-9 : 9′-dianthryl (II) of m. p. 252° but there were also obtained small quantities of 9-benzyl-9 : 10-dihydroanthracene and a stereoisomer of (II) of m. p. 178°. The compound of m. p. 178° was converted into the high-melting form at 200° in a vacuum.

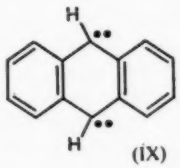
10 : 10′-Dibenzyl-9 : 9′-dianthryl was most easily obtained by a three-stage synthesis from anthrone. When this was treated with benzyl chloride and alcoholic alkali both 10 : 10-dibenzylanthrone and 9-benzyl-10-benzyloxyanthracene were produced. The latter compound was converted by dilute acid into 10-benzylanthrone which was reduced with zinc in hydrochloric acid to 10 : 10′-dibenzyl-9 : 9′-dianthryl.

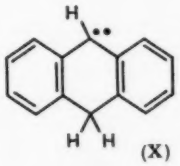
As an alternative approach to the synthesis of benzyl-substituted 9 : 10-dihydroanthracenes we have investigated the reactions of benzyl chloride with the sodium and lithium adducts of anthracene. The structures of these and similar complexes involving other aromatic hydrocarbons have recently been discussed by several groups of workers. Ubbelohde and his colleagues [8] have prepared solid sodium–anthracene complexes and have found them to contain between 1·1 and 2·1 metal atoms per molecule of hydrocarbon. This result accords with the work of Mikhailov and Chernova [9] who estimated the ratio of metal atoms to hydrocarbon molecules in the solid complexes of anthracene with sodium and lithium to be 2 : 1. An analysis of similar complexes in solution has shown that they contain one atom of metal per molecule of hydrocarbon and it has been postulated [10] that complex formation involves the transfer of one electron to the aromatic molecule which thus becomes a radical-ion (VIII). Such a structure is consistent with the results of the investigation of the polarographic half-wave potentials and reduction potentials [11] of aromatic compounds.

Magnetic-susceptibility measurements [12] provide an explanation for the lack of agreement between the analytical results, for it was found that the sodium–anthracene complex, as normally prepared, was paramagnetic, but that prolonged treatment of the adduct with an excess of sodium gave the diamagnetic, bivalent anion (IX).

These conclusions are relevant to the interpretation of our results, for we found that the reaction between benzyl chloride and the sodium–anthracene adduct in ether gave anthracene, dibenzyl, 9 : 10-dihydroanthracene, 9-benzyl-9 : 10-dihydroanthracene (XI),


(VIII)


(IX)


(X)

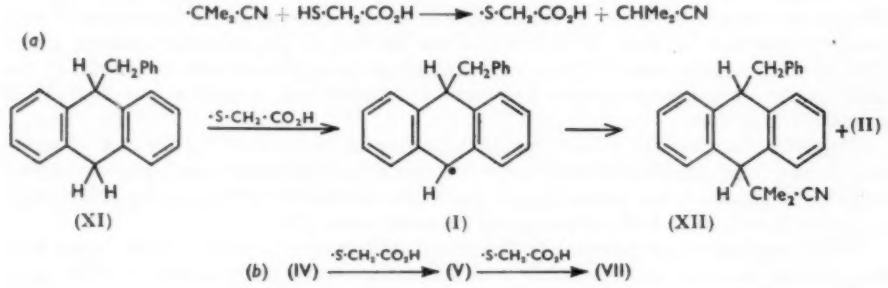
and 9 : 10-dibenzyl-9 : 10-dihydroanthracene (IV), the formation of which products is consistent with the scheme proposed [10] for the reactions of radical-ions. However, we could not detect any dianthryl derivatives such as would be expected to result on a free-radical mechanism.

The lithium–anthracene adduct was formed by treatment of 9 : 10-dihydroanthracene

[8] Holmes-Walker and Ubbelohde, *J.*, 1954, 720; Gracey and Ubbelohde, *J.*, 1955, 4089.
[9] Mikhailov and Chernova, *Doklady Akad. Nauk S.S.S.R.*, 1950, **74**, 939 (*Chem. Abs.*, 1951, **45**, 4698).
[10] Paul, Lipkin, and Weissman, *J. Amer. Chem. Soc.*, 1956, **78**, 116.
[11] Hoijtink, Van Schooten, De Boer, and Aalsbersberg, *Rec. Trav. chim.*, 1954, **73**, 355; Hoijtink, De Boer, Van der Meij, and Wiejland, *ibid.*, 1955, **74**, 277.
[12] Chu and Yu, *J. Amer. Chem.Soc.*, 1954, **76**, 3367.

with butyl-lithium,[13] a method which should lead to the anions (IX) and (X) rather than to the radical-ion (VIII). However, the nature of the products from the reaction of this adduct with benzyl chloride, which produced the same compounds as were obtained from the sodium adduct plus a small amount of 9 : 9 : 10-tribenzyl-9 : 10-dihydroanthracene (VI), indicates that this reaction must also proceed, to a certain extent, by a free-radical mechanism.

The identification of many of the above-mentioned derivatives of 9 : 10-dihydroanthracene was frequently complicated by the ease with which they were decomposed on attempted dehydrogenation. Thus 9 : 9 : 10-tribenzyl-9 : 10-dihydroanthracene (VI), when heated with sulphur, gave 9 : 10-dibenzylanthracene (VII), and 10 : 10′-dibenzyl-9 : 9′ : 10 : 10′-tetrahydro-9 : 9′-dianthryl (II) was converted into 9-benzylanthracene by treatment with chloranil in boiling phenetole. In an attempt to find a method of dehydrogenation that would proceed at temperatures well below that sufficient to cause homolysis of carbon–carbon bonds we have now investigated the reactions of 9-benzyl- and 9 : 10-dibenzyl-9 : 10-dihydroanthracene with the radicals formed by the decomposition of αα′-azo-*iso*butyronitrile in benzene containing mercaptoacetic acid. This reagent was chosen because of the discovery by Bickel and Kooyman [14] that thiyl radicals, produced by the reaction between 2-cyano-2-propyl radicals and thiols, can dehydrogenate 9 : 10-dihydroanthracene although 2-cyano-2-propyl radicals alone are ineffective. Mercaptoacetic acid is a particularly convenient catalyst, for it can easily be removed from the reaction mixture by extraction with alkali.



When 9-benzyl-9 : 10-dihydroanthracene, αα′-azo*iso*butyronitrile, and mercaptoacetic acid were heated in benzene the products were 9-benzyl-10-(2-cyano-2-propyl)-9 : 10-dihydroanthracene (XII) and two stereoisomers of 10 : 10′-dibenzyl-9 : 9′ : 10 : 10′-tetrahydro-9 : 9′-dianthryl (II). The reaction which must involve the intermediate radical (I) evidently proceeds by the mechanism indicated. When 9 : 10-dibenzyl-9 : 10-dihydroanthracene was similarly treated with thiyl radicals, 9 : 10-dibenzylanthracene (VII) was produced. This result indicates that the intermediate radical (V) is sterically prevented from coupling with another radical and therefore is converted into the fully aromatic compound by loss of a second hydrogen atom.

Experimental

*Reaction of Anthracene with Di-*tert.*-butyl Peroxide in Cumene.*—(a) *At reflux temperature.* Anthracene (6·0 g.; purified by distillation with ethylene glycol) [15] and di-*tert.*-butyl peroxide (6 g.) were refluxed in purified cumene (100 ml.), under nitrogen, for 24 hr. The mixture was

[13] Mikhailov and Blokhina, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1949, 279 (*Chem. Abs.*, 1950, **44**, 2963).
[14] Bickel and Kooyman, *Nature*, 1952, **170**, 211.
[15] Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., 1941, p. 345, footnote.

then fractionally distilled and there was obtained *tert.*-butyl alcohol, b. p. 78—81° (4·1 g.), but neither acetone nor unchanged peroxide. When the temperature of the vapours rose to 120° the remaining solution was cooled and kept overnight at 0°. Anthracene (2·5 g.) was collected and the filtrate was steam-distilled until all the solvent had been removed. The residual oil (9·5 g.), in light petroleum (b. p. 40—60°), was chromatographed on alumina. There were isolated 2 : 3-dimethyl-2 : 3-diphenylbutane (4·1 g.; eluted with light petroleum), m. p. and mixed m. p. 119°, anthracene (2·9 g.; eluted with 4 : 1 light petroleum–benzene), and oils (total 2·1 g.); total recoveries were *tert.*-butyl alcohol 60%, 2 : 3-dimethyl-2 : 3-diphenylbutane 36%, and anthracene 90%.

(*b*) *At* 100°. A solution of anthracene (5·0 g.) and di-*tert.*-butyl peroxide (6 g.) in cumene (50 ml.) was heated on the water-bath for 14 days and the product was then worked up as in (*a*), to give 2 : 3-dimethyl-2 : 3-diphenylbutane (1·2 g.) and anthracene (4·8 g., 96%).

*Reaction of Anthracene with Di-*tert.*-butyl Peroxide in Toluene.*—Anthracene (5·0 g.) and di-*tert.*-butyl peroxide (7 g., 1·7 equivs.) in purified toluene (150 ml.) were refluxed, under nitrogen, for 8 days. An attempt was then made to isolate low-boiling products by fractional distillation but the temperature of the vapour rose immediately to 110°. The solvent was removed under reduced pressure and the oily residue was extracted thrice with hot light petroleum (3 × 100 ml.). The insoluble material (1·8 g.) crystallised from benzene in needles, m. p. 252° (Found: C, 93·45; H, 6·4. $C_{42}H_{34}$ requires C, 93·6; H, 6·4%). When dehydrogenated with chloranil in phenetole it gave 9-benzylanthracene (yield 60%). Comparison with an authentic specimen (see below) identified this compound as 10 : 10′-*dibenzyl*-9 : 9′ : 10 : 10′-*tetrahydro*-9 : 9′-*dianthryl*.

The petroleum-soluble material (9·0 g.) was chromatographed on alumina. Light petroleum eluted dibenzyl (0·2 g.), m. p. 52°, and 6 : 1 light petroleum–benzene eluted an oil which was separated into three crystalline products: (i) Colourless needles (from methanol) of 9 : 10-dibenzyl-9 : 10-dihydroanthracene (2·1 g.), m. p. 119°. (ii) Colourless rods (1·9 g.) (from ethanol), m. p. 175° (Found: C, 92·9; H, 6·8. $C_{35}H_{30}$ requires C, 93·3; H, 6·7%). This compound showed ultraviolet light absorption similar to that of 9 : 10-dibenzyl-9 : 10-dihydroanthracene and was dehydrogenated with sulphur to 9 : 10-dibenzylanthracene; it was not isomerised by treatment with butyl-lithium or sodium hydride; comparison with the synthesised compound showed it to be 9 : 9 : 10-*tribenzyl*-9 : 10-*dihydroanthracene*. (iii) Pale yellow needles (from methyl acetate) of 9 : 10-dibenzylanthracene (0·5 g.), m. p. 248°.

Continued elution of the column yielded 9 : 10-dibenzylanthracene (0·4 g.) and 10 : 10′-dibenzyl-9 : 9′ : 10 : 10′-tetrahydro-9 : 9′-dianthryl (0·4 g.).

The total yields of products were: dibenzyl, 0·2 g.; 9 : 10-dibenzylanthracene, 0·9 g. (9%); 9 : 10-dibenzyl-9 : 10-dihydroanthracene, 2·1 g. (21%); 9 : 9 : 10-tribenzyl-9 : 10-dihydroanthracene, 1·9 g. (15%); 10 : 10′-dibenzyl-9 : 9′ : 10 : 10′-tetrahydro-9 : 9′-dianthryl, 2·2 g. (29%).

Preparation of Reference Compounds.—9-*Benzylanthracene*.[16] Anthrone (7·0 g.) in warm benzene (150 ml.) was added, with vigorous stirring, to a solution of benzylmagnesium chloride (from 10 g. of benzyl chloride in 100 ml. of ether), and the mixture was slowly distilled until all of the ether had been removed (1·5 hr.). The mixture was then treated with 20% hydrochloric acid, and the product was isolated in the usual way. 9-Benzylanthracene crystallised from acetone in pale yellow needles (8·6 g., 89%), m. p. 136°. Light absorption in ethanol: max. at 2575 (ε 127,000), 3325 (ε 3000), 3500 (ε 6100), 3650 (ε 8750), and 3850 Å (ε 8600).

9-*Benzyl*-9 : 10-*dihydroanthracene*.[17] 9-Benzylanthracene (3·3 g.) in toluene (30 ml.) and pentyl alcohol (50 ml.) was refluxed with sodium (4·5 g.) until all the metal had dissolved. The product crystallised from methanol in needles (2·6 g., 78%), m. p. 119° (Found: C, 93·0; H, 6·5. Calc. for $C_{21}H_{18}$: C, 93·3; H, 6·7%). Light absorption in ethanol: max. at 2227 (ε 8350), 2524 (ε 1275), 2669 (ε 1500), and 2720 Å (ε 1310).

9 : 10-Dibenzylanthracene, prepared by Barnett and Cook's method,[18] crystallised from benzene in pale yellow needles, m. p. 248°. Light absorption in $CHCl_3$: max. at 2660 (ε 84,000), 3450 (ε 3500), 3600 (ε 7600), 3800 (ε 13,100), and 4000 Å (ε 13,380). Attempts to prepare this compound from anthraquinone by the same method as for 9 : 10-diethylanthracene [1] gave, in one experiment, a yield of 15%.

[16] Barnett, Cook, and Wiltshire, *J.*, 1927, 1724.
[17] Cook, *J.*, 1926, 2160.
[18] Barnett and Cook, *J.*, 1928, 566.

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9 : 10-*Dibenzyl*-9 : 10-*dihydroanthracene*.[7] 9 : 10-Dibenzylanthracene (1·0 g.) was reduced with sodium in pentyl alcohol. The product crystallised from methanol in rods (0·85 g., 85%), m. p. 119° (Found : C, 92·8; H, 6·2. Calc. for $C_{28}H_{24}$: C, 93·3; H, 6·7%). Light absorption in EtOH : max. at 2265 (ε 9350), 2600 (ε 1210), 2655 (ε 1410), and 2720 Å (ε 1070).

The same compound was obtained when 9 : 10-dibenzylanthracene was reduced with sodium in liquid ammonia. It was not isomerised by treatment with sodium hydride or with sodamide. It was dehydrogenated by sulphur at 230° to 9 : 10-dibenzylanthracene.

Benzylation of anthrone. Anthrone (10 g.) and benzyl chloride (20 g.) in methanol (70 ml.) were refluxed under nitrogen while a solution of potassium hydroxide (9·5 g.) in methanol (50 ml.) was added dropwise with stirring. After the addition (30 min.) the mixture was refluxed for 15 min., cooled, and filtered. The residue of 10 : 10-dibenzylanthrone [19] crystallised from benzene in rhombs (12·2 g., 63%), m. p. 229° (Found : C, 90·05; H, 6·1. Calc. for $C_{28}H_{22}O$: C, 89·8; H, 5·9%). Light absorption in $CHCl_3$: max. at 2700 Å (ε 15,900). Reduction of this compound with aluminium amalgam in benzene–ethanol gave a 20% yield of 9 : 9-*dibenzyl*-9 : 10-*dihydro*-10-*hydroxyanthracene* which crystallised from ethanol in pale yellow plates, m. p. 172° (Found : C, 89·4; H, 6·75. $C_{28}H_{24}O$ requires C, 89·3; H, 6·4%). Light absorption in EtOH : max. at 2650 Å (ε 1770).

The filtrate was diluted with water and the precipitate was crystallised from ethanol. 9-*Benzyl*-10-*benzyloxyanthracene* (3·2 g., 16%) formed yellow rods, m. p. 137° (Found : C, 89·7; H, 5·7. $C_{28}H_{22}O$ requires C, 89·8; H, 5·9%). Light absorption in EtOH : max. at 2650 (ε 92,500), 3640 (ε 6800), 3820 (ε 10,600), and 4050 Å (ε 9550).

When the above experiment was conducted with molar equivalents of anthrone (7·0 g.), sodium ethoxide, and benzyl chloride in ethanol there were isolated 10 : 10-dibenzylanthrone (3·3 g., 19%) and 9-benzyl-10-benzyloxyanthracene (1·2 g., 7%).

10-*Benzylanthrone*.[20] 9-Benzyl-10-benzyloxyanthracene (2·5 g.) in acetic acid (30 ml.) was refluxed while concentrated hydrochloric acid (6 ml.) was added dropwise. After the addition (1 hr.) the mixture was refluxed for 1·5 hr., cooled, and poured into iced water. The oil, which solidified on scratching, was crystallised from ether–light petroleum. 10-Benzylanthrone (2·0 g., 85%) formed rods, m. p. 92° (Found : C, 88·35; H, 5·9. Calc. for $C_{21}H_{16}O$: C, 88·7; H, 5·7%). Light absorption in EtOH : max. at 2700 Å (ε 15,000).

9 : 9-Dibenzyl-9 : 10-dihydroanthracene,[7] prepared by the reduction of 10 : 10-dibenzylanthrone with sodium in pentyl alcohol, crystallised from methyl acetate in rods (yield, 82%), m. p. 184° (Found : C, 93·1; H, 6·9%). Light absorption in EtOH : max. at 2670 Å (ε 995).

9 : 9 : 10-Tribenzyl-9 : 10-dihydroanthracene was prepared by reduction of 9 : 9 : 10-tribenzyl-9 : 10-dihydro-10-hydroxyanthracene [18] (1·2 g.) with sodium in pentyl alcohol. It crystallised from acetone in rods (1·0 g., 83%), m. p. 175° (Found : C, 92·9; H, 6·8%). Light absorption in EtOH : max. at 2650 (ε 1450) and 2750 Å (ε 920).

Reaction of dianthron-9-yl with benzylmagnesium chloride. Powdered dianthron-9-yl [21] (1·0 g.) was added to benzylmagnesium chloride solution (prepared from 2·8 g. of benzyl chloride in 100 ml. of ether), and the mixture was refluxed, with stirring, under nitrogen for 2 hr. Benzene (100 ml.) was added and the mixture was slowly distilled until all of the ether had been removed (1·5 hr.). The excess of Grignard reagent was destroyed with dilute acid, and the benzene solution was evaporated to dryness. The products, which were separated chromatographically, were dibenzyl (0·4 g.) and 9-benzylanthracene (0·76 g., 55%).

10 : 10′-*Dibenzyl*-9 : 9′-*dianthryl*. (*a*) 9-Bromo-10-benzylanthracene [17] (5·0 g.), activated magnesium (0·5 g.), and ether (50 ml.) were mixed together under nitrogen. A drop of methyl iodide was added to start the reaction and the mixture was then refluxed, with stirring, for 16 hr. Anhydrous ferric chloride (2·5 g.) was then added and the heating was continued for a further 2 hr. After the addition of an excess of 20% hydrochloric acid, the precipitate was collected, washed with ether, then with methanol, and crystallised from benzene. 10 : 10′-*Dibenzyl*-9 : 9′-*dianthryl* (0·8 g., 21%) formed yellow prisms, m. p. >330° (Found : C, 94·0; H, 5·6. $C_{42}H_{30}$ requires C, 94·35; H, 5·65%). Light absorption in $CHCl_3$: max. at 2530 (ε 148,000), 3450 (ε 5650), 3625 (ε 12,050), 3825 (ε 24,000), and 4050 Å (ε 32,000).

(*b*) 10-Benzylanthrone (1·8 g.) in acetic acid (20 ml.) was refluxed while zinc powder (3 g.) and concentrated hydrochloric acid (4 ml.) were added in small portions. After the addition

[19] Hallgarten, *Ber.*, 1888, **21**, 2508.
[20] Julian and Magnani, *J. Amer. Chem. Soc.*, 1934, **56**, 2174.
[21] Barnett and Matthews, *J.*, 1923, **123**, 380.

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(1 hr.) the mixture was refluxed for 10 min. and then filtered while still hot. The residue, when crystallised from benzene, formed prisms (0·8 g., 47%) identical with the product obtained by method (*a*).

10 : 10′-*Dibenzyl*-9 : 9′ : 10 : 10′-*tetrahydro*-9 : 9′-*dianthryl*. Sodium (2 g.) and pentyl alcohol (25 ml.) were added to a suspension of 10 : 10′-dibenzyl-9 : 9′-dianthryl (0·3 g.) in boiling toluene (30 ml.), and the mixture was refluxed until all of the metal had dissolved (2·5 hr.). During this time the dianthryl dissolved and the solution became colourless. After cooling, the mixture was washed with dilute hydrochloric acid, and the solvent was removed under reduced pressure. When the residue was crystallised from benzene–ethanol the tetrahydro-compound was obtained in colourless prisms (0·17 g., 55%), m. p. 252° (Found : C, 93·8; H, 6·2%). Light absorption in EtOH : max. at 2650 A (ε 1400).

Fractional crystallisation of the mother-liquor yielded 9-benzyl-9 : 10-dihydroanthracene (70 mg., 14%), m. p. 119°, and colourless needles (50 mg., 10%), m. p. 178°, of a *stereoisomer* of 10 : 10′-dibenzyl-9 : 9′ : 10 : 10′-tetrahydro-9 : 9′-dianthryl (Found : C, 93·7; H, 6·4%). The latter showed maximum light absorption at 2650 Å (ε 2450). When heated in an evacuated tube at 200° for 5 min. it was converted into the isomer, m. p. 252°.

When 10 : 10′-dibenzyl-9 : 9′-dianthryl was reduced with sodium in boiling pentyl alcohol the only product was 9-benzyl-9 : 10-dihydroanthracene.

Reaction of the Sodium–Anthracene Adduct with Benzyl Chloride.—Anthracene (3·7 g.), sodium (2·0 g., in small pellets), and broken glass were shaken together in ether (50 ml.) under nitrogen. After 70 hr. the blue solution was filtered through glass wool, and benzyl chloride was added dropwise with stirring until the colour changed to yellow. After addition of water the mixture was filtered to remove anthracene (1·1 g.), and the ethereal solution was taken to dryness under reduced pressure. The residual oil was treated with hot light petroleum and, after removal of the insoluble anthracene (0·4 g.), chromatographed on alumina. The following products were obtained : dibenzyl, 1·9 g.; 9-benzyl-9 : 10-dihydroanthracene, 0·9 g. (16%); 9 : 10-dibenzyl-9 : 10-dihydroanthracene, 1·0 g. (13%); 9 : 10-dihydroanthracene, 0·5 g. (14%).

Reaction of the Lithium–Anthracene Adduct with Benzyl Chloride.—9 : 10-Dihydroanthracene [22] (2·0 g.) was added to a filtered solution of butyl-lithium (prepared from 0·7 g. of lithium and 3·9 g. of *n*-butyl chloride in 30 ml. of ether) and shaken at room temperature under nitrogen for 16 hr. Benzyl chloride was then added dropwise with stirring until the colour of the mixture changed to yellow. Water was added and the precipitate of anthracene (0·2 g.) was collected. The ethereal layer was evaporated to dryness and the residue, in light petroleum, was chromatographed on alumina. Light petroleum eluted successively dibenzyl (1·4 g.) and 9 : 10-dihydroanthracene (0·6 g., 30%). 3 : 1 Light petroleum–benzene eluted an oily mixture (1·7 g.) which was re-chromatographed. The fractions obtained were : (*a*) 9-benzyl-9 : 10-dihydroanthracene (0·2 g., 7%), eluted with light petroleum; (*b*) 9 : 10-dibenzyl-9 : 10-dihydroanthracene (0·8 g., 20%); (*c*) 9 : 9 : 10-tribenzyl-9 : 10-dihydroanthracene (0·2 g., 4%), m. p. and mixed m. p. 175°.

Reaction of 9-*Benzyl*-9 : 10-*dihydroanthracene with Mercaptoacetic Acid and* αα′-*Azoisobutyronitrile.*—9-Benzyl-9 : 10-dihydroanthracene (1·0 g.), mercaptoacetic acid (1·1 g.), and the azo-compound (0·9 g.) in dry benzene (20 ml.) were refluxed under nitrogen for 4 hr. The mixture was then cooled, extracted with aqueous sodium hydrogen carbonate, and washed with water. After removal of the solvent (vacuum) the crude product was treated with hot methanol. The insoluble material crystallised from benzene in needles, m. p. 252°, of the high-melting isomer of 10 : 10′-dibenzyl-9 : 9′ : 10 : 10′-tetrahydro-9 : 9′-dianthryl (260 mg., 26%).

The methanol-soluble material was chromatographed on alumina. The compounds isolated were : (*a*) 9-benzyl-9 : 10-dihydroanthracene (0·32 g.), eluted with 3 : 1 light petroleum–benzene; (*b*) the stereoisomer, m. p. 178°, of 10 : 10′-dibenzyl-9 : 9′ : 10 : 10′-tetrahydro-9 : 9′-dianthryl (40 mg., 4%), eluted with 1 : 1 light petroleum–benzene; (*c*) 9-*benzyl*-10-(2-*cyano*-2-*propyl*)-9 : 10-*dihydroanthracene* which crystallised from ether–light petroleum in colourless needles (180 mg., 14%), m. p. 134° (Found : C, 89·3; H, 7·0; N, 4·05. $C_{25}H_{23}N$ requires C, 89·0; H, 6·9; N, 4·15%). Light absorption in EtOH : max. at 2640 Å (ε 1300). The infrared spectrum showed absorption bands characteristic of the nitrile group.

Reaction of 9 : 10-*Dibenzyl*-9 : 10-*dihydroanthracene with Mercaptoacetic Acid and* αα′-*Azoisobutyronitrile.*—9 : 10-Dibenzyl-9 : 10-dihydroanthracene (340 mg.), mercaptoacetic acid (2 g.),

[22] Bamberger and Lodter, *Ber.*, 1887, **20**, 3073.

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and the azo-compound (0·8 g.) in benzene (30 ml.) were refluxed under nitrogen for 5 hr. The products, which were isolated as in the previous experiment, were 9 : 10-dibenzylanthracene (180 mg., 55%), m. p. 248°, and tetramethylsuccinonitrile (80 mg.), m. p. and mixed m. p. 167°.

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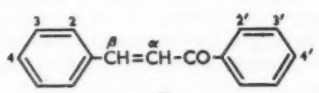
196. *Chalcones and Related Compounds. Part I. Preparation of Nitro-, Amino-, and Halogeno-chalcones.*

By W. DAVEY and J. R. GWILT.

Preparation of mononitrochalcones by an improved method is described and the mononitration of chalcone has been investigated. Amino- and halogeno-chalcones have been prepared by various methods and the most satisfactory preparative conditions established.

CHALCONE (I) (ω-benzylideneacetophenone) and substituted chalcones have been prepared and certain reactions of this typical αβ-unsaturated ketone system studied. The results will be described in this and in subsequent publications. Preliminary studies were devoted to the establishment of the optimum preparative conditions for substituted chalcones and, whilst condensation of the appropriate benzaldehyde and acetophenone in aqueous ethanol by means of sodium hydroxide [1] represents the most satisfactory approach, dismutation of uncondensed aldehyde occurs under strongly alkaline conditions, particularly with the nitrobenzaldehydes.[2] Since magnesium hydroxide suspensions [3] or aqueous sodium carbonate failed to effect condensation, dismutation has been minimised by the use of benzylidene diacetates, prepared by the addition of acetic anhydride to the benzaldehyde in presence of phosphoric acid,[4] and good yields of chalcones, free from gums, have been obtained. At least 1·5 equivalents of sodium hydroxide, relative to diacetate, were necessary for high yields, and in the preparation of cinnamylideneacetophenone at least 3 equivalents of alkali, relative to cinnamylidene diacetate, were necessary. The results obtained are given in Table 1. 2-Nitrochalcone was less pure than the other nitrochalcones, but the very ready dismutation of *o*-nitrobenzaldehyde made use of the diacetate essential.

Nitration of chalcone with nitric acid in acetic anhydride at low temperatures on a somewhat larger scale than that used by previous workers [5] yielded a mixture of 2- and 4-nitrochalcone, together with some oil. Solubility studies showed that ether or benzene was a suitable solvent to separate these isomers and a mixed melting point curve for mixtures of the two isomers was prepared. Attempts to identify 2-nitrochalcone by indigo formation [3, 6] were not successful.



(I)

The direct condensation [1] of aminobenzaldehydes with acetophenones, or of benzaldehydes with aminoacetophenones, gives impure products.[7] Protection of the aldehyde group by diacetate formation in the alkaline condensation gave gums from which low

[1] *Org. Synth.*, Coll. Vol. I, 2nd Edn., p. 78.
[2] Davey and Gwilt, *J.*, 1950, 204.
[3] *Idem, J. Soc. Chem. Ind.*, 1950, **69**, 330.
[4] *Idem, J.*, 1955, 1385.
[5] Goldschmidt, *Ber.*, 1895, **28**, 986; Tanasescu and Georgescu, *J. prakt. Chem.*, 1934, **139**, 189; Le Fèvre, Markham, and Pearson, *J.*, 1933, 344.
[6] Shriner and Kurosawa, *J. Amer. Chem. Soc.*, 1930, **52**, 2538; Janovsky, *Ber.*, 1891, **24**, 971; Best and Nicholson, *Ind. Eng. Chem. Anal.*, 1935, **7**, 190.
[7] Giua and Bagiella, *Gazzetta*, 1921, **51**, II, 116; Scholtz and Huber, *Ber.*, 1904, **37**, 392.

yields (23—44%) of aminochalcones were extracted by hot mineral acid. By the use of acetylation to protect the amino-group, alkaline condensation has been achieved in satisfactory yields (68—84%). Ease of hydrolysis of acetamido-groups in the resulting chalcones varied markedly with their position.

Aminochalcones were also prepared by reduction of the nitrochalcones and a comparative study of reduction methods was made for 3-nitrochalcone; yields were <40%

TABLE 1. *Alkaline condensation of diacetates with acetophenone.*

Diacetate	Ratio NaOH/diacetate (equivs./mole)	Yield (%)	Diacetate	Ratio NaOH/diacetate (equivs./mole)	Yield (%)
Benzylidene ...	2·6	92	*o*-Nitrobenzylidene	0·6	0
	6·5	88		2·8	78
Cinnamylidene	2·3	0	*m*-Nitrobenzylidene	1·1	10
	3·0	58		1·8	92
			p-Nitrobenzylidene	0·6	53
				2·7	100

(iron–acetic acid), 46% (neutral iron,[8] increased to 51% by preforming ferrous chloride), 51% (ferrous hydroxide[9]), 44% (sodium hydrogen sulphide[10]), and 76% (stannous chloride–hydrochloric acid.[11]). The stannous chloride–hydrochloric acid reduction was also the most satisfactory route for the other nitrochalcones, 52—79% yields being obtained, depending on the position of the nitro-group. Aminochalcones were obtained from the stannichlorides by treatment with excess of ammonia solution, followed by extraction with benzene[12] or preferably acetone.[13] Overall yields of aminochalcones from the nitrobenzaldehyde or nitroacetophenone are shown in Table 2, stannous chloride–hydrochloric acid–acetic acid reduction being the most satisfactory procedure.

TABLE 2. *Yields (%) of aminochalcones by various routes.*

Amino-chalcone	By reduction of nitro-chalcone	By alkaline condensation		Amino-chalcone	By reduction of nitro-chalcone	By alkaline condensation	
		NH_2-group protected	NH_2-group not protected			NH_2-group protected	NH_2-group not protected
2-	41	—	16	2′-	45	—	10
3-	73	76	33	3′-	75	63	50
4-	79	23	11	4′-	54	(84) *	(31) *

* Calc. on *p*-aminoacetophenone, prepared from acetanilide by a method similar to that of Kaslow, Genzer, and Goodspeed (*Proc. Indiana Acad. Sci.*, 1950, **59**, 139; *Chem. Abs.*, 1951, **45**, 8534).

TABLE 3. *Yields (%) of halogenochalcones from amines by diazotisation in hydrochloric or phosphoric acid.*

Aminochalcone	Halogenochalcone	HCl	H_3PO_4	Aminochalcone	Halogenochalcone	HCl	H_3PO_4
3-Amino-	3-Chloro-	—	46	3′-Amino-	3′-Chloro-	18	52
4-Amino-	4-Chloro-	33	—	,,	3′-Bromo-	6-	36
,,	4-Bromo-	—	57	4′-Amino-	4′-Chloro-	29	57
,,	4-Iodo-	47	—	,,	4′-Bromo-	51	54

Dankova *et al.*[14] reported m. p. 96—97° for 2-aminochalcone and m. p. 119—120° for its hydrochloride, but the present authors have found m. p. 115° for the free amine while attempts to prepare a hydrochloride yielded resins (m. p. >300°). In some instances, reduction of 3-nitrochalcone by iron and acetic acid gave a product, m. p. 147°, which appeared to be a labile form of 3-aminochalcone, m. p. 159°; two hydrochlorides, m. p. 186° and 198°, were obtained, each of which yielded the stable aminochalcone (m. p. 159°)

[8] West, *J.*, 1925, 494.
[9] *Org. Synth.*, Coll. Vol. III, p. 56.
[10] Haworth and Lapworth, *J.*, 1922, 76.
[11] Dilthey and Berres, *J. prakt. Chem.*, 1925, **111**, 340.
[12] Pfeiffer, *Annalen*, 1925, **441**, 228.
[13] Rupe and Porai-Koschitz, *Z. Farbst. Ind.*, 1906, **5**, 317.
[14] Dankova, Bokova, Preobrazhenskii, Petreshenko, Il'shtein, and Shvetsov, *Zhur. obshchei Khim.*, 1951, **21**, 787.

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TABLE 4. *Overall yields (%) of halogenochalcones (based on original nitrobenzaldehyde or nitroacetophenone) by various routes.*

Chalcone	*via* Amine and diazotisation: Aminochalcone not isolated	*via* Amine and diazotisation: Aminochalcone pre-isolated	Halogeno-benzaldehyde or -acetophenone and alkaline condensation
3-Chloro-	48	35	71
3-Bromo-	27	—	62
4-Chloro-	—	26	49
4-Bromo-	—	45	53
4-Iodo-	—	37	52
3′-Chloro-	48	39	89
3′-Bromo-	30	27	61
4′-Chloro-	—	31	71
4′-Bromo-	35	38	49

TABLE 5. *Effect of the nature and position of certain substituents on the melting points of corresponding chalcones.*

(Italic figures denote new compounds).

Subst. position	Substituent: Cl	Br	I	NO_2	NH_2	Subst. position	Substituent: Cl	Br	I	NO_2	NH_2
2	*52°*	*72°*	*80°*	124°	*115°*	2′	94°	Oil	*113°*	124°	147°
3	75	84	*90*	148	159	3′	*93*	*94*[b]	*85*	129	*124*
4	114	123	*137*	164	151	4′	100	104	*115*	146	108

with aqueous ammonia. Mannich and Dannehl [15] have described a labile form of 2-aminochalcone, but in the present work only the stable form was obtained. Two forms of 3-acetamidochalcone, m. p. 104° [13] and m. p. 119°,[16] have been reported; in the present work the form of lower m. p. was obtained from the alkaline condensation of *m*-acetamidobenzaldehyde and acetophenone.

Decomposition of chalcone diazonium salts gave somewhat low yields of halogenochalcones (Table 3) and the most satisfactory route to these compounds was *via* the appropriate halogeno-benzaldehyde or -acetophenone, followed by the usual alkaline condensation (Table 4). Table 5 details the melting points now obtained for all the *ar*-monohalogenochalcones, together with those for the nitro- and amino-compounds, and suggests some semblance of order in these melting points.

EXPERIMENTAL

m-*Aminobenzaldehyde*.—(*a*) *m*-Nitrobenzaldehyde (10 g.) was reduced by stannous chloride–hydrochloric acid,[17] and the precipitated stannichloride treated with excess of ammonia (*d* 0·88). The residue was washed with 10% aqueous ammonia until chloride-free and extracted with ether. Removal of the ether yielded 6·1 g. (76%) of *m*-aminobenzaldehyde, m. p. indeterminate. Borsche and Sell [18] claim a crystalline form, m. p. 28—30°; other workers have obtained only the amorphous polymer.

(*b*) A freshly prepared mixture of sodium sulphide solution (50 g. in 50 ml. of water) and hydrochloric acid (25 ml.; *d* 1·18) was added to a solution of *m*-nitrobenzaldehyde (20 g.) in 95% (v/v) alcohol (140 ml.). Next morning, the bulk of the alcohol was distilled off and excess of water added. The gummy product was purified by dissolution in hydrochloric acid and reprecipitation with ammonia to yield 5·6 g. (35%) of *m*-aminobenzaldehyde.

(*c*) *m*-Nitrobenzaldehyde (13 g.) was dissolved in acetic acid (*d* 1·05; 50 ml.), water (360 ml.) and degreased activated iron powder (20 g.) were added, and the mixture was heated on the water-bath for 8 hr. The amine was isolated and purified in the usual way (4·7 g., 45%).

(*d*) Calcium chloride (10 g. of dihydrate in 15 ml. of water) and zinc dust (150 g.) were

[15] Mannich and Dannehl, *Ber.*, 1938, **71**, *B*, 1899.
[16] Kaufmann and Burckhardt, *ibid.*, 1913, **46**, 3812.
[17] *Org. Synth.*, Coll. Vol. II, p. 130.
[18] Borsche and Sell, *Ber.*, 1950, **83**, 78.

added to a solution of *m*-nitrobenzaldehyde (15 g.) in 78% (v/v) alcohol (500 ml.), and the mixture refluxed for 1·5 hr. The solution was filtered, the bulk of the alcohol distilled off, and the amine precipitated with water, to yield 5·1 g. (43%) of *m*-aminobenzaldehyde as a gum-free yellow powder, melting over the range 83—155°.

The aldehyde (5 g.) was dissolved in acetic anhydride (25 ml.) and stirred with phosphoric acid (2 ml.; *d* 1·75) at 60° for 1 hr., then kept overnight at room temperature, and diluted with water to yield 5·0 g. (76%) of *m*-acetamidobenzaldehyde, m. p. 82° (Friedländer and Fritsch [19] give m. p. 84°).

o-Acetamidoacetophenone (5·3 g., 81%) was obtained by heating the amine (5 g.) for 0·5 hr. with acetic anhydride (15 ml.) and had m. p. 76°. Gevekoht [20] gave m. p. 76—77°.

m-*Aminoacetophenone.*—(*a*) Reduction of *m*-nitroacetophenone (10 g.) in 25%(w/v) acetic acid (400 ml.) with electrolytic iron powder (20 g.; 80—150 mesh) for 8 hr. on the water-bath, followed by addition of excess of alkali and steam-distillation, yielded 5·5 g. (68%) of *m*-amino-acetophenone, m. p. 97°. Elson *et al.*[21] gave m. p. 98—99° (see also Morgan *et al.*[22] and Phillips [23]).

(*b*) Reduction of *m*-nitroacetophenone (10 g.) with ferrous sulphate (150 g. of heptahydrate in 250 ml. of water) and ammonia (55 ml.; *d* 0·88) under reflux for 1 hr., followed by steam-distillation, yielded 5·7 g. (71%), m. p. and mixed m. p. 97°.

(*c*) Reduction of *m*-nitroacetophenone (10 g.) by Morgan and Moss's method [22] yielded 6·7 g. (82%), m. p. and mixed m. p. 97°.

The amine (4·6 g.), refluxed with acetic acid (10 ml.) and acetic anhydride (20 ml.) for 0·5 hr., yielded *m*-acetoamidoacetophenone (5·4 g., 92%), m. p. 127°. Rupe *et al.*[24] gave m. p. 128—129°.

p-*Acetamidoacetophenone.*—(*a*) Acetanilide (10 g.) and zinc chloride (25 g.) were refluxed in acetic anhydride (100 ml.) for 1·5 hr., then poured into water. The resulting black oil was extracted repeatedly with boiling water and alcohol, to yield *p*-acetamidoacetophenone (4·0 g., 30%), m. p. 169° (Raiford *et al.*[25] gave m. p. 169°; cf. Klingel [26] and Kunckell [27]).

(*b*) Acetanilide (25 g.) in carbon disulphide (250 ml.) was refluxed with acetyl chloride (50 ml.) and aluminium chloride (100 g.) for 8 hr. The carbon disulphide was decanted off and the residue treated with water, to yield the ketone (25 g., 76%), m. p. and mixed m. p. 169°.

p-*Aminoacetophenone.*—The preceding acetyl derivative (10 g.) was refluxed for 1 hr. with N-sodium hydroxide (100 ml.), neutralised, and left overnight to yield *p*-aminoacetophenone (3·5 g., 69%), m. p. 106° (Drewsen [28] gave m. p. 106°; cf. Kaslow *et al.*[29]).

Preparation of Chalcone.—To benzylidene diacetate (10 g.) and acetophenone (7 g.) in 95% alcohol (100 ml.) 10% (w/v) sodium hydroxide solution (50 ml.) was added with stirring and, after 30 min., diluted with water (800 ml.). The precipitated chalcone (9·2 g., 92%) had m. p. and mixed m. p. 56° *Org. Synth.*[1] gives m. p. 55—57°).

Increase of alkali concentration to 50% gave a reduced yield (8·8 g., 88%; m. p. 55°).

The standard method [1] using benzaldehyde gave a yield of 92% (m. p. 55°).

Preparation of Nitrochalcones.—(a) *From nitrobenzaldehydes.* By the standard method,[1] from nitrobenzaldehyde (10 g.) and acetophenone (9 g.) with the other materials *pro rata.*

(b) *From nitrobenzylidene diacetates.* The diacetate (10 g.) was suspended in a solution of acetophenone (5 g.) in 95% alcohol (60 ml.), and 20% (w/v) sodium hydroxide solution (20 ml.) was added slowly. The mixture was stirred for 15 min., diluted with about 2 vols. of water, acidified with hydrochloric acid, and filtered. 2- and 3-Nitrochalcone were recrystallised from aqueous acetic acid, other nitrochalcones from alcohol or aqueous alcohol.

Yields and m. p.s are given in Table 6.

[19] Friedländer and Fritsch, *Monatsh.*, 1903, **24**, 1.
[20] Gevekoht, *Ber.*, 1882, **15**, 2083.
[21] Elson, Gibson, and Johnston, *J.*, 1930, 1128.
[22] Morgan and Moss, *J. Soc. Chem. Ind.*, 1923, **42**, 461T.
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TABLE 6. *Yields of nitrochalcones.*

Posn. of NO_2	Yield (%) from: aldehyde	diacetate	M. p.	Yield (%)	Published results (refs. in parentheses) M. p.
2-	(48)	78	128—130°	46 (*a*)	119—120° to 126° (14, *b*—*d*)
3-	96	92	148	—	120°, 145—146° (*c*, *d*)
4-	94	100	164	79 (*a*)	150°, 163·5°, 164° (*d*, *e*)
2′-	87	91	124	—	124° to 129° (*d*, *f*, *g*)
3′-	97	99	129	—	110°, 125—127°, 131° (*d*, *e*, *g*, *h*)
4′-	92	95	146	—	146·5—147° to 150° (*d*, *g*, *i*)

(*a*) Dippy and Lewis, *Rec. Trav. chim.*, 1937, **56**, 1000. (*b*) Tanasescu and Baciu, *Bull. Soc. chim. France*, 1937, **4**, 1742. (*c*) Sorge, *Ber.*, 1902, **35**, 1067. (*d*) Weygand and Schacher, *Ber.*, 1935, **68**, 2498. (*e*) Le Fèvre *et al.*, see ref. 5. (*f*) Engler and Dorant, *Ber.*, 1895, **28**, 2500. (*g*) Dilthey, Neuhaus, and Schommer, *J. prakt. Chem.*, 1929, **123**, 235. (*h*) Barnes and Dodson, *J. Amer. Chem. Soc.*, 1943, **65**, 1585. (*i*) Weygand, *Annalen*, 1927, **459**, 115.

Cinnamylidene Diacetate.—Cinnamaldehyde (11 g.) was added during 5 min. to a stirred mixture of acetic anhydride (80 ml.) and phosphoric acid (2 ml.; *d* 1·75). The whole was poured into water. The diacetate, which solidified, was filtered off (yield, 19·0 g., 97%) and had m. p. 86° (Späth [30] gave m. p. 86°). A slight yellow colour was removed by washing the product with a little ice-cold alcohol (no change in m. p.).

Cinnamylideneacetophenone.—(*a*) From cinnamylidene diacetate, by the same method as for nitrochalcones, cinnamylideneacetophenone was obtained in 58% yield, with m. p. 97°, rising to 102° on one recrystallisation from aqueous ethanol. Stobbe and Rucker [31] give m. p. 102—103°.

(*b*) From cinnamaldehyde by the same method, the acetophenone was obtained in 84% yield, with m. p. 93°, rising to 102° on one recrystallisation.

Nitration of Chalcone.—To chalcone (50 g.), in acetic anhydride (500 ml.) containing phosphoric acid (5 ml.; *d* 1·75) at −5°, nitric acid (35 ml.; *d* 1·52) was added at such a rate that the temperature did not exceed −5°. Stirring was continued for 30 min. at −5° and the mixture poured into ice-water (5 l.). The precipitated oil (~56 g.) was washed with a little cold ethanol, leaving 47 g. of material, m. p. 124°. Fractionation from ethanol yielded only 2- (m. p. and mixed m. p. 128°) and 4-nitrochalcone [m. p. 160°; m. p. (from benzene) and mixed m. p. 164°]. From the mixed m. p. curve the relative proportions of the 2- and 4-nitrochalcone were approximately 60 : 40. Hence overall yields were: 2-nitrochalcone 46%, 4-nitrochalcone 31%, unidentified material 23%.

2- and 4-Nitrochalcone form a eutectic mixture approximately in the ratio 70 : 30, with m. p. 112°.

Solubilities of 2- and 4-nitrochalcones were determined by evaporating known amounts of saturated solutions, with the following results (g./100 ml.): in C_6H_6 at 20°, 2- 3·7, 4- 0·7; in C_6H_6 at 40°, 2- 5·1, 4- 1·8; in ether at 20°, 2- 1·0, 4- 0·13.

Aminochalcones by Direct Condensation.—Generally, the methods used for the preparation of nitrochalcones (see above) proved successful except that the crude products contained much gum. This was extracted with hot 2N-hydrochloric acid, and the aminochalcones were reprecipitated by addition of 2N-sodium hydroxide to the cold solution and recrystallised from alcohol (charcoal) (see Table 2).

Although Borsche and Sell [18] claim to have obtained crystalline *m*-aminobenzaldehyde, it proved possible to prepare only the usual polymeric form, insoluble in alcohol. Accordingly for direct condensation the aldehyde (1·0 g.) was first dissolved in 5N-hydrochloric acid (10 ml.), and acetophenone (1·1 g.) in 95% alcohol (40 ml. v/v) was added. 10% (w/v) Sodium hydroxide solution (*ca.* 25 ml.) was added to basify the mixture which was then kept at 50° for 45 min. and left overnight at 20°. Filtration yielded 1·6 g. of gum. Extraction with hydrochloric acid followed by reprecipitation and recrystallisation from alcohol (charcoal) yielded 0·8 g. (44%) of 3-aminochalcone, m. p. and mixed m. p. 159°. Rupe and Porai-Koschitz [15] gave m. p. 159°.

The standard method [1] was also used for the preparation of aminochalcones from acetamidoacetophenones (see Table 2).

Hydrolysis of Acetamidochalcones.—(a) *3-Aminochalcone.* The acetyl compound (5 g.) was

[30] Späth, *Monatsh.*, 1915, **36**, 29.
[31] Stobbe and Rucker, *Ber.*, 1911, **44**, 869.

refluxed for 30 min. with a slight excess of 2N-sodium hydroxide, further quantities being added as required to maintain a slightly alkaline reaction. Cooling the mixture yielded 3·8 g. (90%) of 3-aminochalcone, m. p. (from alcohol) and mixed m. p. 159°.

(b) 4-*Aminochalcone*. Alkaline condensation of *p*-acetamidobenzylidene diacetate (5 g.) and acetophenone (2·5 g.) by the standard method [1] yielded a mixture of 4-aminochalcone and its acetyl derivative. The mixture was refluxed with 2N-sodium hydroxide as above, to yield 3·4 g. (68% referred to the diacetate) of 4-aminochalcone, m. p. 151° (from alcohol). Rupe and Porai-Koschitz [13] gave m. p. 151°.

(c) 4′-*Aminochalcone*. Procedure as for the 4-amino-compound gave an 84% yield (from *p*-acetamidoacetophenone), m. p. and mixed m. p. 106°. Scholtz and Huber,[7] and Dilthey *et al.*[32] gave m. p. 108°.

Reduction of Nitrochalcones.—The nitrochalcone (10 g.) was stirred with stannous chloride (40 g. of the dihydrate) and hydrochloric acid (100 ml.; *d* 1·18) and slowly warmed to 90°. The mixture was then generally homogeneous. The solution was left overnight at 0° and the stannichloride compound filtered off. It was mixed with excess of aqueous ammonia and the resultant paste drained at the pump and extracted with boiling acetone. The solvent was removed at room temperature and the residual chalcone recrystallised from alcohol (see Table 2).

2-*Aminochalcone*. 2-Nitrochalcone (5 g.) yielded 2-*aminochalcone* (2·3 g., 52%), m. p. 115° (Found: N, 6·2. $C_{15}H_{13}ON$ requires N, 6·3%). Dankova *et al.*[14] give m. p. 96—97° but their analytical figures do not confirm their having obtained this amine.

3-*Aminochalcone*. A form of m. p. 159° was obtained by reduction of 3-nitrochalcone as above. In some runs by the method of Marrian, Russell, and Todd [33] material (about 35%), m. p. 147° (from alcohol), was obtained. This had mixed m. p. 158° with authentic 3-aminochalcone of m. p. 159°, and mixed m. p. 120—125° with the original 3-nitrochalcone of m. p. 148°. This *form* was readily soluble in mineral acids (Found: C, 80·5; N, 6·3. $C_{15}H_{13}ON$ requires C, 80·7; N, 6·3%).

2N-Hydrochloric acid at 40° was saturated with 3-aminochalcone of m. p. 159°. When the filtrate was left at room temperature colourless plates of the *hydrochloride* were deposited, having m. p. 198° (from water) (Found: Cl^-, 13·9. $C_{15}H_{13}ON,HCl$ requires Cl, 13·7%). Addition of excess of ammonia yielded 3-aminochalcone, m. p. and mixed m. p. 159°. This (higher-melting) hydrochloride was also obtained on boiling the lower-melting amine with 2N-hydrochloric acid.

2N-Hydrochloric acid was saturated with 3-aminochalcone of m. p. 147° at room temperature. On storage, an amorphous *hydrochloride* was deposited, of m. p. 186° (Found: Cl^-, 13·8%). A mixed m. p. with the higher-melting form was 198°. Shaking this salt with excess of ammonia yielded 3-aminochalcone, m. p. and mixed m. p. 159°. Adams, Cohen, and Rees [34] obtained a crude hydrochloride, m. p. 185—195° (decomp.), as the first product in the catalytic hydrogenation of 3-nitrochalcone.

3′-*Acetamidochalcone*.—*m*-Acetamidoacetophenone (5 g.) was dissolved in alcohol (20 ml.; 95% v/v) containing benzaldehyde (4 g.). 2N-Sodium hydroxide (5 ml.) was added and the mixture stirred at room temperature for 30 min., then just neutralised with 5N-hydrochloric acid, and most of the alcohol was distilled off, yielding 3′-*acetamidochalcone* (5·9 g., 92%), m. p. 138° (from alcohol) (Found: N, 5·4. $C_{17}H_{15}O_2N$ requires N, 5·3%). 3′-Aminochalcone, prepared by ferrous hydroxide reduction of 3′-nitrochalcone, was acetylated by boiling acetic anhydride: the m. p. and mixed m. p. with the above material were 138°.

3′-*Aminochalcone*.—3′-Acetamidochalcone (5 g.) was refluxed with a 2% aqueous suspension (50 ml.) of magnesium hydroxide for 1 hr., neutralised with 2N-sulphuric acid, and cooled, to yield 3′-*aminochalcone* (4·0 g., 98%), m. p. 124° (Found: N, 6·2. $C_{15}H_{13}ON$ requires N, 6·3%). This was also prepared by direct condensation of *m*-aminoacetophenone with benzaldehyde or benzylidene diacetate (yields 40% and 61% respectively), and by reduction of 3′-nitrochalcone with iron–acetic acid [32] (yield 26%), ferrous hydroxide [9] (yield 36%), or stannous chloride–hydrochloric acid as above (yield 78%). After recrystallisation all samples had m. p. and mixed m. p. 124°.

Halogenochalcones from Nitrochalcones.—(a) *Chlorochalcones*. Stannous chloride (80 g. of the dihydrate) in hydrochloric acid (100 ml.; *d* 1·16) was refluxed with the nitrochalcone

[32] Dilthey, Neuhaus, Reis, and Schommer, *J. prakt. Chem.*, 1930, **124**, 81.
[33] Marrian, Russell, and Todd, *J.*, 1947, 1419.
[34] Adams, Cohen, and Rees, *J. Amer. Chem. Soc.*, 1927, **49**, 1097.

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(10 g.) for 30 min., then left overnight at room temperature. Diazotisation at 0—5° with sodium nitrite (10 g. in 30 ml. of water) and treatment with cuprous chloride–hydrochloric acid gave little nitrogen, and a mixture of chlorochalcone and amine stannichloride (*ca.* 12 g.) was obtained from which chloro- and amino-chalcones were extracted by hot acetone.

TABLE 7. *Preparation of known halogenochalcones by alkaline condensation.*

Chalcone	Yield (%)	M. p.	Refs.	Chalcone	Yield (%)	M. p.	Refs.
2-Chloro-	83	52°	*a, b*	3-Bromo-	93	84°	*h*
3-Chloro-	94	75	*b, c*	4-Bromo-	99	123	*a*
4-Chloro-	89	114	*b, d, e*, 25	2′-Bromo-	62	Oil	*i*
4′-Chloro-	87	100	*e, f, g*	4′-Bromo-	94	104	*e—h, j*

(*a*) Weygand and Gunther, *Annalen*, 1927, **459**, 118; Pfeiffer and Kunze, *J. prakt. Chem.*, 1928, **119**, 119; Bickel, *J. Amer. Chem. Soc.*, 1946, **68**, 865. (*b*) Ref. *a* of Table 6. (*c*) Eaton, Black, and Fuson, *J. Amer. Chem. Soc.*, 1934, **56**, 687. (*d*) Von Walther and Raetze, *J. prakt. Chem.*, 1902, **65**, 280; Weitz and Scheffer, *Ber.*, 1921, **54**, 2339. (*e*) Dilthey, *J. prakt. Chem.*, 1921, **101**, 202; *f*, Allen and Frame, *Canad. J. Res.*, 1932, **6**, 605. (*g*) Brandstätter, *Monatsh.*, 1949, **80**, 1. (*h*) Stevens, *J.*, 1930, 2107. (*i*) Barnes and Payton, *J. Amer. Chem. Soc.*, 1936, **58**, 1300. (*j*) Kohler, Heritage, and Burnley, *Amer. Chem. J.*, 1910, **44**, 67.

TABLE 8. *New halogenochalcones and "mixed" chalcones.*

Chalcone	M. p.	Yield (%)	Found (%) Hal	Required (%) Hal	Chalcone	M. p.	Yield (%)	Found (%) Hal	Found (%) N	Required (%) Hal	Required (%) N
2′-Chloro-	94°	76	14·4	14·6	4′-Iodo-	115°	94	37·8	—	38·0	—
3′-Chloro-	93	96	14·3	14·6	4′-Bromo-2-chloro-	106	99	22·0 *	—	22·1	—
2-Bromo-	(72)	—	29·1	27·9	4 : 4′-Di-iodo-	216	91	54·7	—	55·2	—
3′-Bromo-	94	94	27·5	27·9	2-Chloro-3′-nitro-...	152	74	12·2	4·8	12·3	4·9
2-Iodo- ...	80	78	37·3	38·0	4′-Bromo-3-nitro-	172	93	24·0	4·1	24·1	4·2
3-Iodo- ...	90	92	37·9	38·0	4′-Chloro-3-nitro-...	145	90	12·3	4·7	12·3	4·9
4-Iodo- ...	137	92	37·9	38·0	4′-Chloro-4-nitro-...	164 †	92	12·3	4·8	12·3	4·9
2′-Iodo- ...	113	53	38·4	38·0	4-Dimethylamino-						
3′-Iodo- ...	85	89	37·7	38·0	3′-nitro-	170	89	—	9·3	—	9·5

* Total halogen, as Cl. † Mixed m. p. *ca.* 148° with 4-nitrochalcone (m. p. 164°).

(b) *Bromochalcones.* Reduction of nitrochalcones by stannous bromide–hydrobromic acid, diazotisation, and decomposition of the diazonium salt with cuprous bromide [17] gave the bromochalcones. The 3-, 3′-, and 4′-bromo-compound were thus obtained in 28, 31, and 38% yield respectively.

(c) *Iodochalcones.* Preliminary results were disappointing and direct condensation was therefore used.

Halogenochalcones from Aminochalcones.—(a) *Diazotisation in hydrochloric acid.* 3′-Aminochalcone (5 g.) in hydrochloric acid (50 ml.; *d* 1·16) was diazotised at 0—5° with sodium nitrite (2 g. in 10 ml. of water), and the solution decomposed by acid cuprous chloride.[17] Extraction of the resulting gum with hot ethanol (charcoal) gave 3′-chlorochalcone (1·0 g., 18%), m. p. and mixed m. p. 92°.

(b) *Diazotisation in phosphoric acid.* 3′-Aminochalcone (5 g.) in phosphoric acid (125 ml.; *d* 1·75) was diazotised by Hodgson and Walker's method,[35] with sodium nitrite (5 g.) in phosphoric acid (100 g.; *d* 1·75), and the diazonium compound decomposed by acid cuprous chloride as before, to yield a product from which 3′-chlorochalcone (3·0 g., 54%), m. p. and mixed m. p. 92°, was extracted. Further results of the use of this method are given in Table 3.

Halogenochalcones by Direct Condensation.—The general method [1] was modified to reduce contamination of the final chalcone. The appropriate aldehyde and acetophenone were dissolved in the minimum amount of ethanol at room temperature, sufficient 2N-sodium hydroxide added to render the stirred solution alkaline, and the whole stirred for 30 min. Neutralisation with 2N-hydrochloric acid was followed by dilution with water and storage overnight. The chalcone was filtered off and recrystallised to constant m. p. from ethanol or acetic acid. Yields were generally above 90% (see Tables 7 and 8).

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[35] Hodgson and Walker, *J.*, 1933, 1620.

197. *Chalcones and Related Compounds. Part II.* Addition of Thiols and Esters to the Chalcone System.*

By W. Davey and J. R. Gwilt.

Addition of thiols and esters usually requires catalysis by alkali. Hydrolysis and decarboxylation of ester adducts from substituted chalcones were not generally successful.

Previous work on the addition of thiols to chalcones has dealt solely with chalcone itself. Addition of toluene-ω-thiol,[1] *p*-thiocresol,[1] or octane-1-thiol [2] has been effected by simple admixture of the compounds, but generally a catalyst is necessary. Dry hydrogen chloride has been used [3] for the addition of ethanethiol or thiophenol, but there is then a tendency for addition at the keto-group as well as at the ethylenic bond. Ruhemann [4] used piperidine to effect the addition of thiophenol or 3-methylbutane-1-thiol to chalcone; this catalyst acts as a strong base in the non-aqueous medium employed and is generally to be preferred to sodium ethoxide, introduced by the same worker; thus Nicolet [5] showed that the adduct from chalcone and thio-*p*-cresol or mercaptoacetic acid is readily hydrolysed by free caustic alkali; consequently, piperidine was generally used in the present work, though diethylamine also proved of value. Addition of mercaptoacetic acid was very difficult to effect, except in the case of 4′-iodochalcone, where good yields were obtained from alcoholic solution in the presence of a little hydrochloric acid.

Acetoacetic ester adducts have previously been obtained from chalcone [6, 7, 8] itself and from hydroxy- or methoxy-chalcones.[9, 10] A catalyst is generally necessary, sodium ethoxide [6, 8] or diethylamine [7] having been used. In the present work, gums were readily formed; in particular, any attempts at acid or alkaline hydrolysis led to intractable oils. Earlier workers have shown that the adducts readily undergo ring closure to cyclic ketones, and it seems probable that the oils now obtained represent mixtures of products of this type.

The addition of malonic ester requires the presence of a catalyst. Piperidine has been used,[11–13] and also sodium methoxide or ethoxide.[12–14] The ethoxides are said to be the more effective, but excess of them may lead to the corresponding enolate, and thence, on hydrolysis, the lactone. The molecular compound between potassium hydroxide and acetaldehyde di*iso*propyl acetal has also been claimed [15] as an effective catalyst. In the present work, diethylamine, piperidine, and sodium ethoxide were used, and yields tended to decrease in that order, generally being rather poor, and much gum was formed. To reduce the possibility of side reactions,[16, 17] a large excess of malonic ester was used.

The adduct of chalcone and malonic ester may be hydrolysed to the dicarboxylic acid, and this on fusion gives carboxymethylchalcone.[18] For the substituted chalcones now studied, it proved essential to purify the adduct as otherwise hydrolysis gave intractable

* Part I, preceding paper.

[1] Nicolet, *J. Amer. Chem. Soc.*, 1935, **57**, 1098.
[2] Frank and Smith, *ibid.*, 1946, **68**, 2103.
[3] Posner, *Ber.*, 1901, **34**, 1395; 1902, **35**, 808.
[4] Ruhemann, *J.*, 1905, **87**, 461.
[5] Nicolet, *J. Amer. Chem. Soc.*, 1931, **53**, 3066.
[6] Knoevenagel, *Annalen*, 1894, **281**, 58.
[7] Knoevenagel and Speyer, *Ber.*, 1902, **35**, 397.
[8] Dieckmann and von Fischer, *Ber.*, 1911, **44**, 969.
[9] Forster and Heilbron, *J.*, 1924, **125**, 340.
[10] Petrow, *Ber.*, 1930, **63**, 898.
[11] Kohler, *Amer. Chem. J.*, 1911, **46**, 481.
[12] Michael and Ross, *J. Amer. Chem. Soc.*, 1932, **54**, 407.
[13] Connor and Andrews, *ibid.*, 1934, **56**, 2715.
[14] Kohler and Conant, *ibid.*, 1917, **39**, 1104.
[15] Weizmann, B.P. 594,182/1947.
[16] Dieckmann and Kron, *Ber.*, 1908, **41**, 1277.
[17] Michael and Ross, *J. Amer. Chem. Soc.*, 1933, **55**, 1632.
[18] Vorländer and Knötzsch, *Annalen*, 1897, **294**, 332.

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gums. Even so, only 4-nitrochalcone gave the corresponding diacid, and this was not satisfactorily decarboxylated. It seems, therefore, that, under the conditions used, side reactions tend to occur rather more readily.

Experimental

Results are summarised in the accompanying Tables.

Addition of Thiols.—(a) *Ethanethiol.* The chalcone (5 g.) was dissolved in the minimum amount of methyl alcohol (3-nitrochalcone required toluene as well), and ethanethiol (1 ml.) and piperidine (2 drops) were added. After 7 days at room temperature the mixture was steam-distilled, and the resultant gum fractionated from alcohol.

Table 1. *Addition of thiols to certain chalcones.*

Chalcone	Thiol *	Catalyst †	Adduct Yield (%)	Adduct M. p.	Found (%) Hal	Found (%) S	Formula	Required (%) Hal	Required (%) S
Unsub.	$CMe_2Et{\cdot}SH$	Pip	87	40°	—	10·0	$C_{26}H_{24}OS$	—	10·3
3-NO_2	PhSH	,,	91	106	*a*	8·7	$C_{21}H_{17}O_3NS$	*a*	8·9
,,	EtSH	,,	—	Gum	—	—	—	—	—
,,	MAA	,,	44	65	—	9·4	$C_{17}H_{15}O_5NS$	—	9·3
,,	,,	$NHEt_2$	Trace	—	—	—	—	—	—
,,	,,	HCl	0	—	—	—	—	—	—
4-NMe_2	PhSH	Pip	83	157	*b*	8·8	$C_{23}H_{23}ONS$	*b*	8·9
,,	MAA	,,	Trace	—	—	—	—	—	—
,,	,,	NEt_2	—	Oil	—	—	—	—	—
4-MeO-4′-Br	$CMe_2Et{\cdot}SH$	Pip	79	140	19·1	7·5	$C_{21}H_{25}O_2SBr$	19·2	7·6
3′-NO_2	PhSH	,,	31	62	*c*	8·8	$C_{21}H_{17}O_3NS$	*c*	8·9
,,	EtSH	,,	—	Oil	—	—	—	—	—
,,	MAA	,,	29	100°	—	9·0	$C_{17}H_{15}O_5NS$	—	9·3
,,	,,	NEt_2	Trace	—	—	—	—	—	—
,,	,,	HCl	0	—	—	—	—	—	—
4′-Br	PhSN	$NHEt_2$	83	114	20·3	7·8	$C_{21}H_{17}OSBr$	20·4	8·0
4′-I	,,	Pip	60	104	28·6	7·2	$C_{21}H_{17}OSI$	28·6	7·2
,,	EtSH	,,	59	92	31·9	7·8	$C_{17}H_{17}OSI$	32·1	8·1
,,	MAA	,,	0	—	—	—	—	—	—
,,	,,	HCl	74	60	29·5	7·4	$C_{17}H_{15}O_3SI$	29·8	7·5

* MAA = Mercaptoacetic acid. † Pip = Piperidine.

a, Found: N, 3·7. Reqd.: N, 3·9%. *b*, Found: N, 3·7. Reqd.: N, 3·9%. *b*, Found: N, 3·8. Reqd.: N, 3·9%.

Table 2. *Addition of esters to chalcones.*

Chalcone Subst.	M. p.	Yield (%) by catalyst Pip *	$NHEt_2$	NaOEt	Adduct, m. p.	Found (%) Hal	Found (%) N	Formula	Required (%) Hal	Required (%) N
With ethyl acetoacetate.										
2-Cl	52°	—	Oil	37	110°	10·2	—	$C_{21}H_{21}O_4Cl$	9·5	—
3-NO_2	148	—	,,	—	—	—	—	—	—	—
3′-NO_2	129	—	,,	85	129	—	3·5	$C_{21}H_{21}O_6N$	—	3·4
4-NMe_2-4′-Cl	50	—	50	144	114	8·8	3·5	$C_{23}H_{26}O_4NCl$	8·5	3·4
4′-Br	104	36	45	Gum	63	17·7	—	$C_{21}H_{21}O_4Br$	18·0	—
4′-I	115	—	67	—	130	27·6	—	$C_{21}H_{21}O_4I$	27·3	—
With ethyl malonate.										
3-NO_2	—	32	52	25	98	—	3·3	$C_{22}H_{23}O_7N$	—	3·4
4-NO_2	164	—	49	Gum	113—114	—	3·6	,,	—	3·4
2′-NO_2	124	—	0	,,	—	—	—	—	—	—
3′-NO_2	—	0	78	29	76	—	3·2	$C_{22}H_{23}O_7N$	—	3·2
4-NMe_2	112·5	38	—	Gum	85	—	3·5	$C_{24}H_{28}O_5N$	—	3·4
4-NMe_2-4′-Cl	—	36	—	,,	114	8·2	3·3	$C_{24}H_{28}O_5NCl$	8·0	3·1
4′-Br	—	36	45	,,	63	17·7	—	$C_{22}H_{23}O_5Br$	19·1	—
4′-I	—	45	—	—	75	25·6	—	$C_{22}H_{23}O_5I$	25·7	—

* Pip = Piperidine.

(b) *Other thiols.* Reactions were generally effected as above, but the mixtures were heated on the water-bath for 1—4 hr. Where the adduct did not readily separate on cooling, the solution was steam-distilled.

Addition of Acetoacetic Ester.—(i) *Catalysis by sodium ethoxide.* Acetoacetic ester (10 ml.)

was mixed with sodium ethoxide (from 2·5 g. of sodium) in absolute ethanol (50 ml.), and the chalcone (5 g.) added. The mixture was heated on the water-bath for 2 hr., neutralised with 5N-hydrochloric acid, and steam-distilled. The crude residue was extracted with alcohol (benzene for the 4′-bromochalcone adduct) in the presence of charcoal. The reaction with 3′-nitrochalcone also yielded a small amount of material melting at 220° (insufficient for analysis).

(ii) *Catalysis by diethylamine or piperidine.* The chalcone (5 g.) was dissolved in the ester (20 ml.), absolute ethanol being added if necessary. The mixture was heated on the water-bath for 2 hr. with the catalyst (5 drops). In the case of diethylamine, further catalyst was added from time to time. The final solution was treated as before.

Addition of Malonic Ester.—This was conducted essentially as for acetoacetic ester, but with a large excess of ester. Steam-distillation readily removed the excess of ester when reaction was complete.

Hydrolysis of Malonic Ester Adducts.—Hydrolysis of adduct mixtures *in situ* with alcoholic potassium hydroxide yielded only intractable oils, and acid hydrolysis gave the original chalcone and ester. Adducts were therefore first separated and purified. A portion (1·0 g.) was then refluxed for 2 hr. with 0·5N-alcoholic potassium hydroxide (20 ml.), the resultant solution acidified with N-hydrochloric acid (20 ml.), and most of the alcohol distilled off. Material separating on cooling was filtered off and recrystallised from alcohol. The adducts from 3- and 3′-nitrochalcone yielded products of m. p. 310° and 195°, respectively, while only gum was obtained from 4′-iodochalcone; in no case was titratable acidity detectable. The adduct from 4-nitrochalcone apparently yielded *dicarboxymethyl-4-nitrochalcone* (0·6 g., 69%) (Found: N, 3·7%; equiv., 182. $C_{18}H_{15}O_7N$ requires N, 3·9%; equiv., 178·5), m. p. (from alcohol) 140°. Cautious fusion yielded only a gum, not completely melted at 320°, and with negligible titratable acidity.

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198. *Chalcones and Related Compounds. Part III.* Addition of Benzene Analogues to the Chalcone System.*

By W. DAVEY and J. R. GWILT.

Addition of benzene to chalcone itself is well known, and the general method has also been used as a route to substituted ββ-diphenylpropiophenones. In the present work, adduct formation was by no means complete, and evidence is put forward for the isomerisation of the chalcones under these conditions.

ββ-DIPHENYLPROPIOPHENONE is readily prepared by addition of benzene to chalcone in the presence of aluminium chloride.[1] Substituents in a benzene nucleus are *generally* in the *para*-position in the corresponding adducts,[2,3] but, in view of possible uncertainty, substituted ββ-diphenylpropiophenones have been usually prepared from chalcones by other routes, particularly by way of the Grignard reaction [4,5] or other organometallic compound.[5,6] Such approaches have their limitations, particularly in preparing the nitro-compounds.

The optimum proportion of aluminium chloride was found experimentally to lie between two and three moles per mole of chalcone, in general agreement with the findings of Dippy and Palluel.[2] The presence of dry hydrogen chloride had no apparent effect, nor did the

* Part II, preceding paper.

[1] *Org. Synth.*, Coll. Vol. II, p. 236.
[2] Dippy and Palluel, *J.*, 1951, 1415.
[3] Dippy and Young, *J.*, 1952, 1817.
[4] Kohler, *Amer. Chem. J.*, 1904, **31**, 642; 1907, **38**, 511.
[5] Cilman and Kirby, *J. Amer. Chem. Soc.*, 1941, **63**, 2046.
[6] Wittig and Bub, *Annalen*, 1950, **566**, 113.

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rate or order of adding the components (cf. Perrier [7]). Increase in temperature led only to tar formation.

Results for the reaction of certain halogeno- and nitro-chalcones with typical benzenoid compounds are summarised in the accompanying Tables. The recovered products were found to consist, in general, of up to four components, as follows: (A) The expected adduct, in yields up to 36%; (B) unchanged chalcone, generally 60—70% (nitrochalcones); (C) the fraction of lowest m. p., in yields of up to 16% from the mother-liquors; (D) small yields (up to 3%) of ash-free material of high m. p. (255—285°).

Experimental

General Method (cf. ref. 1).—The chalcone (5 g.) was dissolved in the benzene analogue (150 ml.) and added to a mixture of aluminium chloride (6—8 g.) and further solvent (100 ml.). (In the reaction between 3-nitrochalcone and benzene, 350 ml. of the latter were required in all.) The mixture was then stirred at 20° until the components were virtually all in solution and then for a further hour. The mixture was filtered, the aluminium chloride addition compounds were decomposed in the usual way, and the solvent was evaporated slowly. The mother-liquors were finally steam-distilled and any residue was examined. Species of indefinite m. p. were further fractionated from alcohol.

Small amounts of material insoluble in the final reaction mixture generally consisted of unchanged chalcone. The insoluble fraction from the reaction between 4-nitrochalcone and chlorobenzene, however, contained 2·0% of chlorine. This was probably due only to strong adsorption of chlorobenzene since the chlorine content fell on washing with alcohol. The m. p. of this fraction was 160° (not sharp), unchanged on admixture with the original 4-nitrochalcone (m. p. 164°).

Discussion

The yields of adduct, though low, are of the same order as those obtained by Dippy and Palluel,[2] and it seems that, with these particular chalcones and under these comparatively mild conditions, the reversible nature of the addition [8] has resulted in equilibrium at a fairly low concentration of adduct. Hence fractions A and B represent the relative proportions in the equilibrium mixture.

Table 1. *Products isolated from the reaction mixtures.*

		M. p. of fraction				Yield (%) of fraction			
Chalcone	Additive	A	B	C	D	A	B	C	D
3-NO_2	PhOMe	178°	146°	124°	280°	22	64	12	2
,,	C_6H_6	190	144	120	285	22	67	8	3
,,	PhCl	200	145	—	—	32	68	0	0
,,	PhMe	180	144	123	255	18	68	12	2
4-NO_2	PhCl	190	161	130	—	20	64	16	0
2′-NO_2	,,	—	124	107	—	0	99	1	0
3′-NO_2	,,	150	129	—	—	36	64	0	0
4′-Br	PhOMe	—	104	96	—	0	95	5	0
4′-I	PhMe	—	115	98	—	0	95	5	0

Material obtained as fraction C had the same analytical figures as the original chalcones but melting points were somewhat lower. The existence of more than one form has previously been reported for chalcone itself [9] and for certain nitro- and halogeno-chalcones.[10] Of the compounds now considered, Weygand and Schacher [11] had reported

[7] Perrier, *Ber.*, 1900, **33**, 815.
[8] Eaton, Black, and Fuson, *J. Amer. Chem. Soc.*, 1934, **56**, 687.
[9] Le Fèvre, *J.*, 1937, 1037.
[10] Davey and Gwilt, Part I, *J.*, 1957, 1008.
[11] Weygand and Schacher, *Ber.*, 1923, **56**, 1144.

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m. p.s of 120°, 145°, and 146° for 3-nitrochalcone and 150° and 163·5° for 4-nitrochalcone, and Brandstätter [12] reported 105°, 101°, and 97° for different forms of 4′-bromochalcone. In the latter instance, the stable form was cooled under controlled conditions, *i.e.*, truly polymorphic forms were obtained.

TABLE 2. *Analyses of adducts and isomers.*

		Adduct (A)			Isomer (C)		
Chalcone	Additive	Found N (%)	Formula	Reqd. N (%)	Found N (%)	Formula	Reqd. N (%)
3-NO_2	PhOMe	3·8	$C_{32}H_{19}O_4N$	3·9	5·5	$C_{15}H_{11}O_3N$	5·5
,,	C_6H_6	4·2	$C_{21}H_{17}O_3N$	4·2	5·4	,,	5·5
,,	PhCl	3·6	$C_{21}H_{16}O_3NCl$ [a]	3·8	—	—	—
,,	PhMe	4·0	$C_{22}H_{19}O_3N$	4·1	5·5	,,	5·5
4-NO_2	PhCl	3·6	$C_{21}H_{16}O_3NCl$ [b]	3·8	5·4	,,	5·5
2′-NO_2	,,	—	—	—	Trace	—	—
3′-NO_2	,,	3·8	,,	3·8	—	—	—
4′-Br	PhOMe	—	—	—	27·6 [d]	$C_{15}H_{11}OBr$	27·9 [d]
4′-I	PhMe	—	—	—	38·9 [d]	$C_{15}H_{11}OI$	38·0 [d]

[a] Found: Cl, 9·6%. [b] Found: Cl, 9·5%. [c] Found: Cl, 9·5% (Reqd. in all cases: Cl, 9·7%). [d] Halogen.

Price and Meister [13] suggest that the following four types of reaction are generally catalysed by the same compounds: (*a*) Friedel–Crafts reactions, (*b*) polymerisation of olefins, (*c*) condensation of olefins with aromatic compounds, and (*d*) *cis–trans*-isomerisation of olefins. They therefore consider that the same active intermediate is common to each of these reactions. It therefore seemed probable that isomerisation of the chalcones had occurred to some extent, and, coincidentally with the completion of our own experimental work, Dippy and his co-workers [14] reported the isomerisation of similar compounds under similar conditions.

In view of these and other more general observations (see, *e.g.*, ref. 15) it therefore appears that the material comprising fraction C (when present) is the *cis*-form of the chalcone while fraction B is the normal (*trans*-)form.

The materials in fraction D (from 3-nitrochalcone only) were insufficient for full analysis. Wittig and his co-workers [16] reported the dimerisation of chalcone. They also showed that further addition may occur between chalcone and certain adducts, and it seems likely that these high-melting compounds are of this type.

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[12] Brandstätter, *Monatsh.*, 1949, **80**, 1.
[13] Price and Meister, *J. Amer. Chem. Soc.*, 1939, **61**, 1595.
[14] Dippy, McGhie, and Young, *Chem. and Ind.*, 1952, 195.
[15] Kipping and Kipping, "Perkin and Kipping's Organic Chemistry," Chambers, London, 1939, p. 640.
[16] Wittig, Meyer, and Lange, *Annalen*, 1951, **571**, 167.

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199. *The Formation of Carbonium Ions by the Action of Metal Salts. Part III.* The Reaction of Mercuric Chloride with Triarylmethyl Chlorides in Nitromethane, Chlorobenzene, and Benzene.*

By J. W. Bayles, Alwyn G. Evans, and J. R. Jones.

Previous work on the ionization of triphenylmethyl chloride by mercuric chloride in nitromethane has been extended to chloro- and methyl-substituted triphenylmethyl chlorides in nitromethane, and to tri-*p*-tolylmethyl chloride in chlorobenzene and benzene. In the nitromethane the following equilibria exist: $RCl + HgCl_2 \rightleftharpoons R^+HgCl_3^-$; $R^+HgCl_3^- \rightleftharpoons R^+ + HgCl_3^-$. The changes in free energy have been obtained for the forward reactions. In this paper, the effect of the nature of R on these free-energy changes is given and discussed.

In the benzene and chlorobenzene, ion pairs, $R^+HgCl_3^-$, are formed but do not dissociate, and their solvation involves mercuric chloride molecules.

Stable crystalline complexes have been obtained from the $RCl–HgCl_2$ solutions in benzene. These complexes contain R^+ ions, as shown by their colour.

A study of the ionization of triphenylmethyl chloride by mercuric chloride in nitromethane [1a,b] showed that the solutions contain triphenylmethyl ions, partly as free ions ($Ph_3C^+ + HgCl_3^-$) and partly as ion pairs ($Ph_3C^+HgCl_3^-$). In this paper we describe a similar investigation of *o*-chloro-, *p*-chloro-, *o*-methyl-, and *p*-methyl-monosubstituted triphenylmethyl chlorides and of tri-*p*-chlorophenylmethyl chloride in nitromethane, and of tri-*p*-tolylmethyl chloride in chlorobenzene and benzene.

Experimental

Materials.—The triarylmethyl chlorides were prepared and purified as described by Evans, Jones, and Osborne,[2] and the m. p.s agreed well with those given by them.

Nitromethane was obtained from L. Light and Co. Ltd., and was purified as described earlier.[2a]

" AnalaR " benzene was obtained from British Drug Houses Ltd. and was dried over sodium wire and fractionated. The middle fraction distilling at 80° was collected.

Commercial chlorobenzene was kept overnight over phosphoric oxide, decanted on to a little fresh phosphoric oxide, and was fractionated from this through an 18 inch point-column; it had b. p. 132°.

Sulphuric acid was the 98% " AnalaR " reagent.

" AnalaR " mercuric chloride was twice sublimed in a high vacuum before use.

Spectra.—The light absorption of the solutions containing mercuric chloride and triarylmethyl chloride was measured on a Unicam S.P. 500 spectrophotometer, with an optical path length of 1 cm. The spectra are shown in Figs. 1*a*—*c*. The spectra of the sulphuric acid solutions of the corresponding alcohols were calculated from results at the concentrations used experimentally, so that the optical densities at the absorption peaks are the same as in the solvent used.

Effect of Concentration.—Master solutions, one of mercuric chloride and the other of triarylmethyl chloride, were mixed in various ratios, and the concentration of carbonium ions in the resulting solution was determined by assuming that $\int D_\lambda d\lambda$ is the same for these solutions as for 98% sulphuric acid solutions containing the same concentration of the carbonium ions. The same value for $\Delta G°$ ($\pm 0{\cdot}1$ kcal./mole) for the equilibria involved was obtained when the concentration of the ions was determined by making the alternative assumption that the height of the absorption peak is the same for these solutions as for 98% sulphuric acid solutions containing the same concentration of carbonium ions. In the nitromethane solutions of the

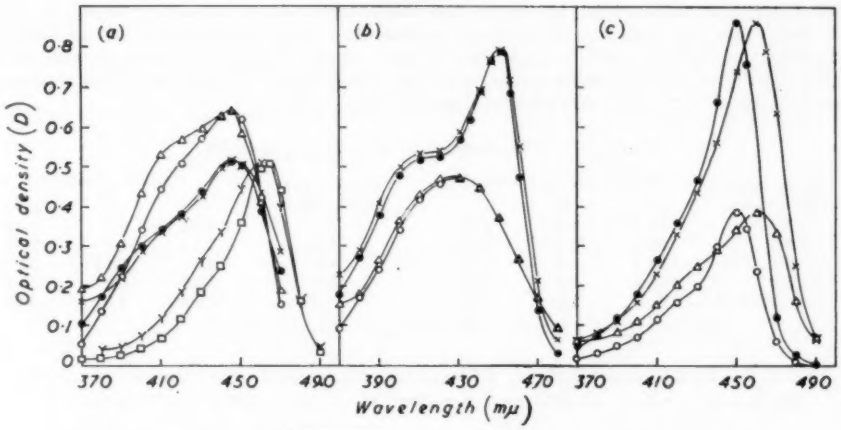
* Part II, Bayles, Cotter, and Evans, *J.*, 1955, 3104.

[1] (*a*) Bentley and Evans, *Research*, 1952, **5**, 535; (*b*) Bayles, Evans, and Jones, *J.*, 1955, 206; (*c*) Bayles, Cotter, and Evans, *J.*, 1955, 3104.

[2] Evans, Jones, and Osborne, (*a*) *Trans. Faraday Soc.*, 1954, **50**, 16, 470; (*b*) *J.*, 1954, 3803.

monosubstituted triphenylmethyl chlorides studied, the absorption peak occurs at the same wavelength as for the corresponding 98% sulphuric acid solution. For tri-*p*-chlorophenylmethyl chloride in nitromethane there is a small hypsochromic peak shift of 4 mμ and for solutions of tri-*p*-tolylmethyl chloride in chlorobenzene and benzene there is a bathochromic peak shift of 10 mμ in each case. In spite of these peak shifts, the shapes of the curves are very similar to those for the corresponding sulphuric acid solutions, so that there is no doubt that we are examining the spectrum of the carbonium ion. It has been shown earlier that the carbonium ion concentration can be determined as described above although there are these peak shifts.[3]

FIGS. 1*a*—*c*.



Compound	Total concn. of triarylmethyl cpd. (10^{-5} mole $l.^{-1}$)	Total concn. of mercuric chloride (10^{-4} mole $l.^{-1}$)	Solvent	Temp.
		FIG. 1*a*.		
○ *p*-Cl·C_6H_4·CPh_2·OH	1·305	—	98% H_2SO_4	
△ *p*-Cl·C_6H_4·CPh_2Cl	57·1	3·24	$MeNO_2$	17°
● *o*-Cl·C_6H_4·CPh_2·OH	1·052	—	98% H_2SO_4	
× *o*-Cl·C_6H_4·CPh_2Cl	25·5	3·035	$MeNO_2$	14
□ (*p*-Cl·C_6H_4)$_3$C·OH	0·495	—	98% H_2SO_4	
Y (*p*-Cl·C_6H_4)$_3$CCl	19·1	8·82	Me·NO_2	15
		FIG. 1*b*.		
○ *o*-Me·C_6H_4·CPh_2·OH	1·40	—	98% H_2SO_4	
△ *o*-Me·C_6H_4·CPh_2·Cl	8·12	0·791	$MeNO_2$	16
● *p*-Me·C_6H_4·CPh_2·OH	1·74	—	98% H_2SO_4	
× *p*-Me·C_6H_4·CPh_2Cl	6·72	0·603	$MeNO_2$	14
		FIG. 1*c*.		
○ (*p*-Me·C_6H_4)$_3$C·OH	0·494	—	98% H_2SO_4	
△ (*p*-Me(C_6H_4)$_3$CCl	640	35·1	C_6H_6	13
● (*p*-Me·C_6H_4)$_3$C·OH	1·102	—	98% H_2SO_4	
× (*p*-Me·C_6H_4)$_3$CCl	36·8	19·0	PhCl	16

Complex between Mercuric Chloride and Triarylmethyl Chloride.—When the benzene solutions of mercuric chloride and triarylmethyl chloride were mixed, the resulting solution was found to be stable during the measurement of its optical density. After about 6 hr., however, a trace of an orange-red complex had crystallized. When such a mixed solution was left to crystallize as much as possible, the supernatant liquid had an optical density of less than 0·1. Thus it was not possible to examine the reaction of mercuric chloride with tri-*p*-tolylmethyl chloride in benzene except under conditions for which the solution was supersaturated with respect to this complex. Since under these conditions no measurable change in optical density occurred for at least 15 min. after the solution had been made up we have confidence in the validity of the results obtained in benzene (which were completed within 5 min. of mixing) for the dependence

[3] Evans, McEwan, Price, and Thomas, *J.*, 1955, 3098.

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of the carbonium-ion concentration on the concentrations of mercuric chloride and triarylmethyl chloride.

In order to examine the complex in more detail, highly concentrated benzene solutions of mercuric chloride and triarylmethyl chloride were mixed, and the composition of the orange-red complex which crystallized was determined as follows. A known weight of the RCl–$HgCl_2$ complex was treated with a known amount of 98% sulphuric acid, the solution decanted from the mercuric sulphate so formed, and the amount of triarylmethyl chloride determined spectrophotometrically, our previously determined values for the extinction coefficients of the triarylmethyl ions being used. (We find that when the triarylmethyl chloride is dissolved in 98% sulphuric acid it is completely converted into carbonium ions.) The results are given in Table 1, together with carbon, hydrogen, and chlorine content of the same complexes. It is seen that these two methods are in good agreement. Using the sulphuric acid method of estimating the $[HgCl_2]$: [RCl] ratio in the complex we determined the effect on this of the $[HgCl_2]$: [RCl] ratio in the solution from which the complex was precipitated. The results are given in Table 2 for the tri-*p*-tolylmethyl chloride–$HgCl_2$ complex.

TABLE 1. *Composition of* RCl–$HgCl_2$ *complex.*

Molar ratio	$(p\text{-Me}\cdot C_6H_4)_3CCl$: Calc. %			Molar ratio	Ph_3CCl : Calc. %		
$HgCl_2$: RCl	C	H	Cl	$HgCl_2$: RCl	C	H	Cl
1	44·6	3·55	17·9	1	41·4	2·7	10·6
2·5	26·4	2·10	21·3	4·5	15·2	1·0	23·6
2·7	25·3	2·0	21·5	4·8	14·4	0·95	23·7
3·0	23·2	1·9	21·8	5·0	13·9	0·9	23·8
Found :	27·2	2·1	22·2	Found :	15·3	1·3	23·7

Ratio by H_2SO_4 method : $(p\text{-Me}\cdot C_6H_4)_3CCl$, 2·7; Ph_3CCl, 4·8.

TABLE 2. *Composition of* $HgCl_2$–RCl *complex precipitated from solutions of varying* $HgCl_2$ *concentrations in benzene.* $[(p\text{-Me}\cdot C_6H_4)_3CCl] = 2{\cdot}013 \times 10^{-3}$ mole $l.^{-1}$.

$[HgCl_2]$ (10^{-3} mole $l.^{-1}$)	3·75	7·49	13·65
Ratio, $HgCl_2$: RCl (molar) ($\pm$ 0·05)	2·45	2·77	2·8

These complexes melted at 90—110° (with decomp.). The tri-*p*-tolylmethyl chloride–mercuric chloride complex crystallized as six-sided plates.

No such complexes were obtained from the nitromethane and chlorobenzene solutions.

Molecular-weight Determination of Mercuric Chloride in Benezene.—A number of cryoscopic experiments were carried out on benzene solutions of mercuric chloride (25 ml. of the solution in a Beckmann freezing-point apparatus). The apparatus was thermally insulated by means of asbestos. The freezing point was read within $\pm$0·005°. Concentrations were used which gave freezing point depressions of 0·03—0·08°. Higher concentrations could not be used owing to the possibility of crystallization of the mercuric chloride, so the accuracy of the molecular-weight determinations was $\pm$50 units. In spite of this, the molecular weights so obtained were in no case greater than that corresponding to $HgCl_2$, showing that there is no measurable association of mercuric chloride in benzene.

DISCUSSION

Nitromethane Solutions.—Stability of solutions. The use of nitromethane as a solvent for these ionization reactions has been criticized by Smith and Leffler [4] on the grounds that when they made up triphenylmethyl chloride solutions in nitromethane the optical density decreased rapidly during 40 min. and a precipitate of ammonium chloride was formed. We always obtained stable solutions, whenever the rigorous method of purification developed in our earlier work was followed.[2a] This stability is strikingly demonstrated in the diagrams given earlier [2a, b] for the temperature-dependence of various triarylmethyl chloride solutions in nitromethane. In these experiments such solutions having optical densities from 0·2 to 0·5 (for an optical path length of 1 cm.) were heated and cooled within the temperature range 15—40° for 2—3 hr., the optical density at any temperature being always reproducible; the solutions remained perfectly clear.

[4] Smith and Leffler, *J. Amer. Chem. Soc.*, 1955, **77**, 1700.

In Part I[1b] temperature-dependence was investigated for mercuric chloride–triphenylmethyl chloride–nitromethane solutions, of optical density 0·2—0·7; these solutions were also heated and cooled within the temperature range of 15—40° for 2—3 hr., and again the optical density at any temperature was reproducible, the solutions remaining clear throughout the experiment.

We have kept a solution of triphenylmethyl chloride in nitromethane sealed in an optical cell for 10 days. The optical density of the solution initially was 0·178, the optical path length being 1 cm. After 10 days the optical density was 0·170, the solution remaining clear throughout the period. The stability of these solutions is further supported by the reproducibility of the results obtained with this solvent, especially the close correlation, discussed later in this paper, between the present values of ΔG°_{1a} for ionization by mercuric chloride in nitromethane, and those obtained previously for ionization in nitromethane in absence of mercuric chloride.

We have found[1c] that, when mercuric bromide is added to a nitromethane solution of

FIG. 2*a*.

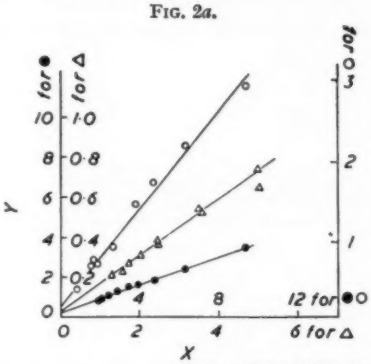

FIG. 2*b*.

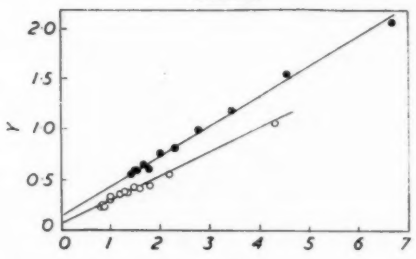

FIG. 2*a*. *Plot of* (X) $10^{-3}/([HgCl_2][RCl])^{\frac{1}{2}}$ (l. mole^{-1}) *against* (Y) $10^{-2}\{[R^+] + [R^+(HgCl_3)^-]\}/([RCl][HgCl_2])$ (l. mole^{-1}).
○ *o*-Cl·C$_6$H$_4$·CPh$_3$Cl. ● *p*-Cl·C$_6$H$_4$·CPh$_3$Cl. △ (*p*-Cl·C$_6$H$_4$)$_3$CCl.

FIG. 2*b*. *Plot of* (X) $10^{-4}/([HgCl_2][RCl])^{\frac{1}{2}}$ (l. mole^{-1}) *against* (Y) $\{[R^+] + [R^+(HgCl_3)^-]\}/([RCl][HgCl_2])$ (l. mole^{-1}).
○ *o*-Me·C$_6$H$_4$·CPh$_3$Cl. ● *p*-Me·C$_6$H$_4$·CPh$_3$Cl.

tri-*p*-tolylmethyl bromide until no further ionization occurs, the bromide is 100% ionized (±15%) if the extinction coefficient obtained for the carbonium ion in sulphuric acid is used. This again supports the stability of the carbonium ions in these solutions.

The results obtained for the ionization of triarylmethyl chlorides in nitromethane are further substantiated by their correlation with the corresponding results in nitroethane, 2-nitropropane, nitrobenzene, and *m*-nitrotoluene.[2a, 5]

Nature of the equilibrium. The curves obtained when the ionic concentration is plotted against the product of the reactant concentrations are of the same form as those obtained for the triphenylmethyl chloride–mercuric chloride system reported earlier.[1b] The points obtained when the mercuric chloride concentration is kept constant and the triarylmethyl chloride concentration is varied fall on the same curve as those found when the triarylmethyl chloride concentration is kept constant for a variation in the mercuric chloride concentration. Thus the reaction producing the carbonium ion is of the same order with respect to each reactant. It is therefore suggested that the equilibria involved are of the same form as those postulated in Part I for triphenylmethyl chloride.[1b]

This is established by the plots shown in Figs. 2*a* and *b*, obtained by analysing the

[5] Evans, Price, and Thomas, *Trans. Faraday Soc.*, 1954, **50**, 568.

results according to these equations as described in Part I. The fact that such good straight lines are obtained for these systems very strongly supports this method of analysis.

In Table 3 are given the mean values for the free-energy changes of reactions (1*a*) and (2*a*) (ΔG°_{1a} and ΔG°_{2a}), obtained from these plots as described in Part I. The variation in

$$RCl + HgCl_2 \underset{b}{\overset{a}{\rightleftharpoons}} R^+HgCl_3^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$R^+HgCl_3^- \underset{b}{\overset{a}{\rightleftharpoons}} R^+ + HgCl_3^- \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

ΔG°_{1a} [the free energy of ion-pair formation according to equation (1)], as substituents are introduced, is given in column 6. It is seen that the introduction of methyl groups increases, whereas that of chlorine atoms reduces, the ease of ion-pair formation, this effect being very marked when three *p*-chlorines are introduced.

In nitromethane, in the absence of mercuric chloride, the carbonium chloride undergoes ion-pair formation, $RCl \rightleftharpoons R^+Cl^-$, without subsequent dissociation of the ion pairs. The effect of substituents on the free-energy change for this ion-pair formation, which was

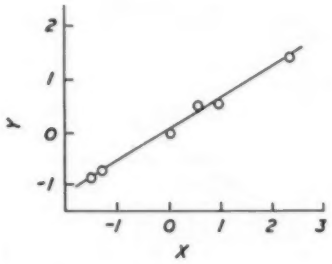

FIG. 3. *Plot of* $(X)\ \Delta G^\circ_{RCl} - \Delta G^\circ_{Ph_3COCl}$ *for* $RCl + HgCl_2 \longrightarrow R^+HgCl_3^-$ *in nitromethane against* $(Y)\ \Delta G^\circ_{RCl} - \Delta G^\circ_{Ph_3COCl}$ *for* $RCl \longrightarrow R^+Cl^-$ *in nitromethane*

measured earlier,[2] is plotted in Fig. 3 against the corresponding values obtained in this paper for the $RCl + HgCl_2 \rightleftharpoons R^+HgCl_3^-$ reaction (Table 3, column 6), and it is seen that there is a very close parallelism between these two sets of values, as is to be expected.

In Table 3, column 7, are given the variations in ΔG°_{2a} [the free energy of dissociation

TABLE 3. *Thermodynamic values for reactions in nitromethane at* 17°.

$$RCl + HgCl_2 \underset{b}{\overset{a}{\rightleftharpoons}} R^+HgCl_2^- \quad . \quad . \quad . \quad (1), \text{ and } R^+HgCl_3^- \underset{b}{\overset{a}{\rightleftharpoons}} R^+ + HgCl_3^- \quad . \quad . \quad . \quad (2)$$

R	Mean K_1 (mole fraction)	Mean K_2 (mole fraction)	Mean ΔG°_{1a} (kcal./mole)	Mean ΔG°_{2a} (kcal./mole)	$(\Delta G^\circ_{1a\,(RCl)} - \Delta G^\circ_{1a\,(Ph_3COCl)})$ (kcal./mole)	$(\Delta G^\circ_{2a\,(RCl)} - \Delta G^\circ_{2a\,(Ph_3COCl)})$ (kcal./mole)
Ph_3C	$1{\cdot}5 \times 10^3$	$1{\cdot}3 \times 10^{-6}$	$-4{\cdot}2 \pm 0{\cdot}2$	$7{\cdot}8 \pm 0{\cdot}6$	0	0
p-Cl·C_6H_4·CPh_3	$4{\cdot}9 \times 10^2$	$1{\cdot}71 \times 10^{-6}$	$-3{\cdot}6 \pm 0{\cdot}2$	$7{\cdot}8 \pm 0{\cdot}6$	$+0{\cdot}6 \pm 0{\cdot}4$	$0 \pm 1{\cdot}2$
o-Cl·C_6H_4·CPh_3	$2{\cdot}67 \times 10^2$	$2{\cdot}11 \times 10^{-7}$	$-3{\cdot}2 \pm 0{\cdot}2$	$9{\cdot}3 \pm 0{\cdot}9$	$+1{\cdot}0 \pm 0{\cdot}4$	$+1{\cdot}5 \pm 1{\cdot}5$
p-Me·C_6H_4·CPh_3	$2{\cdot}14 \times 10^4$	$3{\cdot}95 \times 10^{-6}$	$-5{\cdot}7 \pm 0{\cdot}3$	$7{\cdot}4 \pm 1{\cdot}2$	$-1{\cdot}5 \pm 0{\cdot}5$	$-0{\cdot}4 \pm 1{\cdot}8$
o-Me·C_6H_4·CPh_3	$1{\cdot}65 \times 10^4$	$3{\cdot}45 \times 10^{-6}$	$-5{\cdot}5 \pm 0{\cdot}5$	$7{\cdot}4 \pm 0{\cdot}7$	$-1{\cdot}3 \pm 0{\cdot}7$	$-0{\cdot}4 \pm 1{\cdot}3$
$(p\text{-Cl·}C_6H_4)_3C$ ...	$3{\cdot}0 \times 10^1$	$8{\cdot}02 \times 10^{-6}$	$-1{\cdot}9 \pm 0{\cdot}3$	$6{\cdot}8 \pm 0{\cdot}3$	$+2{\cdot}3 \pm 0{\cdot}5$	$-1{\cdot}0 \pm 0{\cdot}9$

of the ion pairs, according to equation (2)] as substituents are introduced. The error involved in measuring ΔG°_{2a} is greater than that for measuring ΔG°_{1a}, but we see that for the change of R which we have studied there is no parallel change in ΔG°_{2a}. This is to be expected since reaction (1*a*) involves the breaking and forming of bonds and the transfer of an electron, whereas reaction (2*a*) merely involves the separation of the charged bodies. Thus equilibrium (1) should be very markedly affected by a change in R, whereas equilibrium (2) should be independent of R except in so far as substituents in R increase the epuilibrium distance to which the ions can approach each other.

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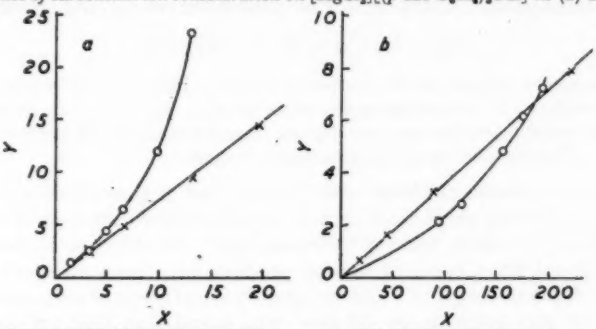
Solutions in Benzene and Chlorobenzene.—The results are shown in Fig. 4 for the tri-*p*-tolylmethyl chloride solutions in chlorobenzene and in benzene. In both solvents the carbonium-ion concentration varies linearly with the concentration of tri-*p*-tolylmethyl chloride when the mercuric chloride concentration is kept constant. This indicates that the ionisation involves only one molecule of tri-*p*-tolylmethyl chloride and, further, that no dissociation of ion pairs can be detected in these solutions since if this occurred the plot would be curved. The plot obtained when the mercuric chloride concentration is varied while the tri-*p*-tolylmethyl chloride concentration is kept constant shows that more than one molecule of mercuric chloride is involved in the reaction. This suggests that the mercuric chloride acts as a solvating agent for the ion pair $R^+HgCl_3^-$ when it is formed in these poorly solvating liquids. A similar effect has been found for the trichloroacetic acid-catalyzed dimerization of 1 : 1-diphenylethylene where, in a poorly ionizing solvent such as benzene, the order in acid is 3, one of these acid molecules being involved in proton

FIG. 4. *Dependence of carbonium ion concentration on* $[HgCl_2][(p\text{-}MeC_6H_4)_3CCl]$ *in* (*a*) PhCl *and* (*b*) C_6H_6.



Plot of (*X*) $10^7[HgCl_2][RCl]$ (*mole*^{2} *l.*$^{-2}$) *against* (*Y*) $10^6\,[R^+(HgCl_3)^-]$ (*g.-ion l.*$^{-1}$).

FIG.	Total tri-*p*-tolylmethyl chloride (10^{-4} mole l.$^{-1}$)	Total mercuric chloride (10^{-4} mole l.$^{-1}$)
4*a*	○, 6·92 (20°)	×, 4·73 (20°)
4*b*	○, 61·2 (17°)	×, 35·1 (13°)

donation to the olefin, and the other two helping to solvate the ion pair so formed.[6] Thus the ionization reaction in benzene and in chlorobenzene solution may be written as :

$$RCl + nHgCl_2 \rightleftharpoons (R^+HgCl_3^-)_{solv.\,(n-1)\,HgCl_2}$$

where $(n - 1)$ molecules of mercuric chloride help in the solvating of the ion pair. The mercuric chloride involved in this solvation is loosely bound and n can on this account have a non-integral value.

There will be an equilibrium constant of the form $K = [\text{ions}]/[RCl][HgCl_2]^n$, and the value of n has been obtained by plotting $\log_{10}$ [ions] against $\log_{10}$ $[HgCl_2]$ for the solutions of constant RCl concentration. In this way the mean value for n is found to be 1·9 for the benzene solutions. In chlorobenzene n is found to increase from 1·0 to 2·4 as the mercuric chloride concentration increases within the limits used in our experiments. It is to be noticed that, although a variation of this kind has not been observed for the benzene solutions, a much smaller range of carbonium-ion concentration has been used in this solvent.

It is seen that the solvents lie in the following order as regards their ability to promote the ionization reaction : nitromethane > chlorobenzene > benzene.

Solid Complexes.—The fact that the crystalline complexes which separate from the

[6] Evans, Jones, and Thomas, *J.*, 1955, 1824.

benzene solutions containing RCl and mercuric chloride are orange-red shows that these crystals are ionic and contain R^+ ions.

Evidence for the tendency of mercuric chloride to associate with the ion pair is found in the composition of these orange-red crystalline complexes. Their analyses show an excess of mercuric chloride over the organic chloride, this excess increasing with increase of mercuric chloride concentration in the mother-liquor containing a given concentation of RCl (see Table 2).

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UNIVERSITY COLLEGE, CARDIFF. [*Received, August 1st,* 1956.]

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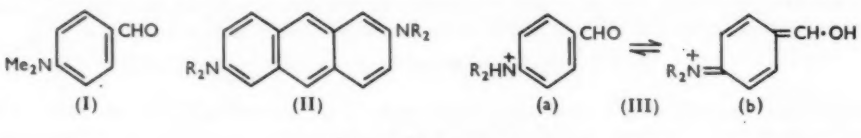
200. *The Action of Tin and Hydrochloric Acid on* p-*Dialkylaminobenzaldehydes. Part I. The Mechanism of the Reaction.*

By FREDERICK H. C. STEWART.

Treatment of *p*-dialkylaminobenzaldehydes with tin and hydrochloric acid produces 2 : 6-bisdialkylaminoanthracenes. The yield of anthracene and the velocity of the reaction depend on the nature of the dialkylamino-group. The mechanism of this reaction is discussed.

REDUCTION of an aromatic aldehyde usually gives one of three main classes of product depending on the reducing agent used, namely, (*a*) toluene derivatives as in the Clemmensen reaction, (*b*) benzyl alcohols, and (*c*) hydrobenzoins. In the case of *p*-dimethylaminobenzaldehyde (I) all three types of normal product have been observed under various conditions with different reagents.[1] An apparently novel mode of reduction has, however, been reported for this aldehyde by Albano [2] who found that with tin and hydrochloric acid at room temperature it gave 2 : 6-bisdimethylaminoanthracene (II; R = Me) in 25% yield. In view of the potential value of this reaction for the synthesis of new anthracene derivatives the mechanism has now been investigated.

Albano suggested that the reaction proceeded through the quinonoid cation (IIIb; R = Me), which is in equilibrium with the normal hydronium cation (IIIa; R = Me), the equilibrium in this case being much displaced in favour of the latter. In support, he



(I) (II) (a) (III) (b) (IV)

pointed out that reduction of the deeply coloured anil hydrochloride (IV), in which the quinonoid form analogous to (IIIb; R = Me) is more important,[3] gave a higher yield of the anthracene (II; R = Me). The behaviour of compound (IV), however, is not strictly comparable with that of *p*-dimethylaminobenzaldehyde (I) in view of the probably considerable effect of differing rates of cleavage of carbon–nitrogen and carbon–oxygen

[1] Schwenk, Papa, Whitman, and Ginsberg, *J. Org. Chem.*, 1944, **9**, 1; Nystrom and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3738; Chaikin and Brown, *ibid.*, 1949, **71**, 122; Allen, *J. Org. Chem.*, 1940, **15**, 435; Clemo and Smith, *J.*, 1928, 2423; Conant and Cutter, *J. Amer. Chem. Soc.*, 1926, **48**, 1016.

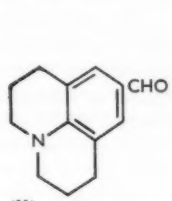
[2] Albano, *Anal. Asoc. Quím. Argentina*, 1946, **34**, 18.

[3] Albano, *ibid.*, 1944, **32**, 43; Madelung, *J. prakt. Chem.*, 1926, **114**, 46.

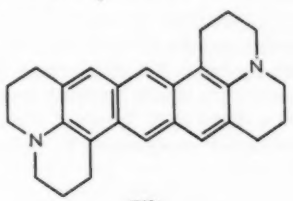
bonds on the course of the reaction, since it is clear that such a cleavage must occur at some stage of the overall reaction. A more suitable compound for comparison with *p*-dimethylaminobenzaldehyde (I) is 8-formyljulolidine (V). In this the conjugative ability of the nitrogen atom is greater than in the dimethylamino-analogue as a result of the coplanarity enforced by the heterocyclic system,[4] which will tend to enhance the stability of the quinonoid form analogous to (IIIb). When the aldehyde (V) was treated with tin and hydrochloric acid it reacted much more rapidly than *p*-dimethylaminobenzaldehyde under the same conditions and gave a 70—75% yield of benzo(1 : 2-7′ : 8′)(4 : 5-7″ : 8″)dijulolidine (VI).

The conjugative ability of the diethylamino-group is less than that of the dimethylamino-group owing to steric inhibition of resonance.[5] Thus diethylaniline is a considerably stronger base (pK_a 6·56) than dimethylaniline (pK_a 5·06) owing to the suppression of base-weakening quinonoid structures in the former. This effect was reflected in the behaviour of *p*-diethylaminobenzaldehyde which reacted very slowly with tin and hydrochloric acid to yield a trace only of 2 : 6-bisdiethylaminoanthracene (II; R = Et). More or less intermediate behaviour was exhibited by *p*-ethylmethylaminobenzaldehyde which reacted more slowly than *p*-dimethylaminobenzaldehyde (I) with formation of 2 : 6-bisethylmethylaminoanthracene in 25% yield. These results indicate the importance for this reaction of mesomeric interaction between the dialkylamino- and formyl groups.

Although *p*-diethylaminobenzaldehyde gave very little 2 : 6-bisdiethylaminoanthracene (II; R = Et) a 20% yield of 2 : 6-bisdiethylamino-9 : 10-dihydro-9 : 10-dihydroxyanthracene (VII; R = Et) was isolated from the reaction mixture. This compound was smoothly converted into 2 : 6-bisdiethylaminoanthracene (II; R = Et) in warm stannous chloride solution. It seemed probable from this result that a diol of this type is an inter-



(V)



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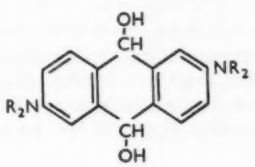

(VII)

mediate in each of these reactions, and this view was supported by isolation of the corresponding diol (VII; R = Me) from a reaction with *p*-dimethylaminobenzaldehyde (I) stopped at a point when the anthracene (II; R = Me) was just beginning to separate as its sparingly soluble tin salt. Like its diethylamino-analogue the diol (VII; R = Me) readily yielded the corresponding anthracene (II; R = Me) with stannous chloride.

The formation of a 2 : 6-bisdialkylamino-9 : 10-dihydro-9 : 10-dihydroxyanthracene (VII) from a quinonoid cation (IIIb) does not involve an overall reduction, but represents a condensation of a relatively familiar type. It resembles the self condensation of 3 : 4-dimethoxybenzyl alcohol derivatives under acid conditions to give 9 : 10-dihydro-2 : 3 : 6 : 7-tetramethoxyanthracene (VIII).[6] A similar reaction is the formation of 2 : 6-bisdimethylamino-9 : 10-dihydroanthracene (IX) from *p*-methoxymethyl-*NN*-dimethylaniline and phenylmagnesium bromide.[7] These condensations can be considered as involving the incipient cations (X) and (XI), respectively, as intermediates.

It is noteworthy that the present condensation is not effected by hydrochloric acid alone, but requires the presence of metallic tin. The formation of the intermediate diol

[4] Smith and Yu, *J. Org. Chem.*, 1952, **17**, 1281.
[5] Brown, McDaniel, and Häfliger, "Determination of Organic Structures by Physical Methods," (Ed. Braude and Nachod) Academic Press, New York, 1955, p. 607.
[6] Robinson, *J.*, 1915, **107**, 267.
[7] Mann and Stewart, *J.*, 1954, 4127.

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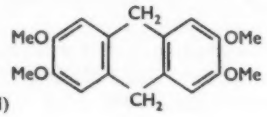
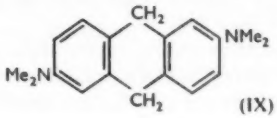
(VII) is possibly a heterogeneous reaction involving the quinonoid cation (IIIb) on the surface of the dissolving tin.

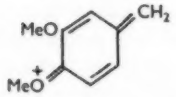
Heating 2 : 6-bisdiethylamino-9 : 10-dihydro-9 : 10-dihydroxyanthracene (VII; R = Et) with hydrochloric acid gave a rather complex mixture from which 2 : 6-bisdiethylaminoanthrone (XII) was isolated in 30% yield. Small amounts of 2 : 6-bisdiethylaminoanthracene (II; R = Et) and a white crystalline substance were also formed. The structure of the last material is uncertain; it has the empirical composition $C_{22}H_{28}ON_2$,



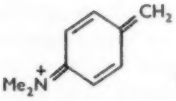
(VIII)



(IX)



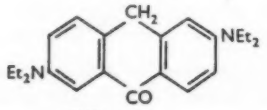
(X)



(XI)

and its infrared spectrum indicates the absence of hydroxyl groups, but a strong peak at 1035 cm.$^{-1}$, which is not found for the anthrone (XII) or 2 : 6-bisdiethylaminoanthracene (II; R = Et), is consistent with the presence of an ether linkage. A possible formulation of the substance as 2 : 6-bisdiethylamino-9 : 10-epoxy-9 : 10-dihydroanthracene (XIII) is scarcely in accord with its stability to boiling hydrochloric acid, since the analogous compound (XIV), prepared by Wittig and Pohmer,[8] is converted into α-naphthol under these conditions.

An outstanding property of 2 : 6-bisdialkylaminoanthracenes is the production of a deep red colour when their dilute acid solutions are treated with various oxidising agents. This colour is irreversibly discharged by heat, but its thermal stability and its intensity are dependent to a marked degree on the particular anthracene used, being least for 2 : 6-bisdiethylaminoanthracene (II; R = Et) and greatest for benzo(1 : 2-7′ : 8′)(4 : 5-7″ : 8″)dijulolidine (VI). From the latter compound, by using hydrogen peroxide in



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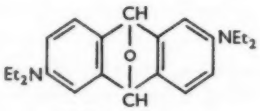
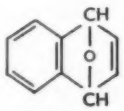


(XIII)



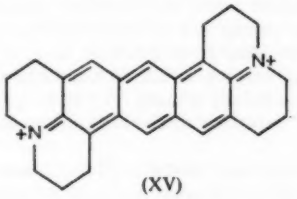
(XIV)

hydrochloric acid as the oxidising agent, it was possible to isolate the coloured product in crystalline form. This was a very soluble blue salt, readily reconverted into (VI) by titanous chloride, and analysing as the tetrahydrate of the dichloride of the di-imonium cation (XV). This structure was supported by the preparation of the corresponding picrate, perchlorate, and chloroplatinate in anhydrous form. The stability of a cation of this type will depend to a large extent on the conjugative ability of the nitrogen atoms. In the case of the cation (XV) the conjugation is probably near its maximum value owing to the enforced coplanarity of the molecule.[4] With the corresponding diethylamino- and dimethylamino-cations (XVI; R = Et and Me) the conjugation of the nitrogen atoms will tend to be weakened, as mentioned earlier, by factors such as steric hindrance and rotation of the amino-groups due to thermal agitation.

These results suggest a possible mechanism for the final stage of the reaction of *p*-dialkylaminobenzaldehydes with tin and hydrochloric acid. The initially formed diol (VII) can be considered as the *pseudo*-base corresponding to the hypothetical hydroxide of the

[8] Wittig and Pohmer, *Angew. Chem.*, 1955, **67**, 348.

di-imonium cation (XVI), and under strongly acid conditions will tend to form a salt of the latter. The resulting cation (XVI) will be rapidly reduced by the stannous chloride present, forming the corresponding anthracene by the uptake of two electrons. The observed appearance of a thermolabile red colour when either of the diols (VII; R = Et or Me) was treated with warm dilute sulphuric acid supports this explanation. The tendency of a diol (VII) to ionise to a cation (XVI) under the action of acids will depend on



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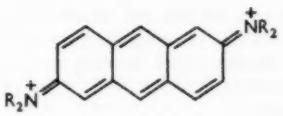

(XVI)

the conjugative ability of the dialkylamino-groups in the manner discussed earlier, and must be considered as an important factor in determining the velocity of the overall reaction. It is possible that this factor may even be more decisive than the stability of Albano's quinonoid intermediate (IIIb).

The application of this reaction to the synthesis of other substituted anthracenes and, in particular, of heterocyclic derivatives such as (VI) is now being studied.

Experimental

Preparation of p-*Dialkylaminobenzaldehydes.*—The aldehydes used have been described in the literature. With the exception of *p*-dimethylaminobenzaldehyde, which was used as the "AnalaR" product, they were made by the *NN*-dimethylformamide–phosphorus oxychloride procedure of Campaigne and Archer [9] which gave the following yields: 8-formyljulolidine [4] (81%), *p*-diethylaminobenzaldehyde [10] (72%), and *p*-ethylmethylaminobenzaldehyde [10] (70%).

Reduction of p-*Dialkylaminobenzaldehydes with Tin and Hydrochloric Acid.*—In order to make the results comparable the following standard conditions were employed. The procedure is somewhat different from that described by Albano.[2]

The aldehyde (5·0 g.) was dissolved in concentrated hydrochloric acid (165 ml.) and water (135 ml.), and granulated tin (20 g.) was added. The mixture was kept at about 40° until the reaction was complete (1—16 days), and the precipitated tin salt filtered off and decomposed with 20% aqueous sodium hydroxide to liberate the crude anthracene, which was dried and extracted with hot benzene. After removal of the benzene the anthracene was recrystallised from a suitable solvent.

(*a*) After 7—8 days *p*-dimethylaminobenzaldehyde (I) gave **2 : 6-bisdimethylaminoanthracene** (II; R = Me), yellow needles (from benzene), m. p. 253—254° (decomp.; rapid heating in sealed tube) (33%). Albano [2] gives m. p. 250° and 25% yield.

(*b*) After 1—2 days 8-formyljulolidine (V) gave *benzo*(1 : 2-7′ : 8′)(4 : 5-7″ : 8″)*dijulolidine* (VI), buff leaflets or yellow needles (from ethanol–benzene), m. p. 221—223° (decomp.) (70—75%) (Found: C, 84·55; H, 8·1; N, 7·7. $C_{26}H_{28}N_2$ requires C, 84·7; H, 7·7; N, 7·6%). Benzene solutions deposited a dark brown solid on exposure to air.

(*c*) After 16 days *p*-ethylmethylaminobenzaldehyde gave **2 : 6-*bisethylmethylaminoanthracene***, yellow crystals (from benzene–ethanol), m. p. 167—168° (25%) (Found: C, 81·9; H, 8·7; N, 9·4. $C_{30}H_{34}N_2$ requires C, 82·2; H, 8·3; N, 9·6%).

Dilute benzene solutions of these anthracenes exhibited a strong blue fluorescence.

Preparation of **2 : 6-*Bisdialkylamino*-9 : 10-*dihydro*-9 : 10-*dihydroxyanthracenes.***—(*a*) The reaction mixture from *p*-diethylaminobenzaldehyde (10 g.) with concentrated hydrochloric acid (330 ml.), water (270 ml.), and tin (40 g.) was set aside for 14 days, filtered, and diluted with water, and the tin was precipitated with hydrogen sulphide. The filtered solution was made

[9] Campaigne and Archer, *J. Amer. Chem. Soc.*, 1953, **75**, 989.
[10] Duff, *J.*, 1945, 276.

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alkaline and extracted with benzene and ether. Evaporation of the dried extracts and treatment of the oily residue with light petroleum (b. p. 100—120°) gave 2 : 6-*bisdiethylamino*-9 : 10-*dihydro*-9 : 10-*dihydroxyanthracene* (VII; R = Et), which recrystallised from light petroleum (b. p. 100—120°) in needles, m. p. 118·5—120° (2·2 g., 22%) (Found: C, 74·2; H, 8·7; N, 8·05. $C_{22}H_{30}O_2N_2$ requires C, 74·5; H, 8·5; N, 7·9%).

The diol (VII; R = Et) (0·5 g.) was heated with a solution of tin (6 g.) in hydrochloric acid (90 ml.; 1 : 1 v/v) for 2 hr. on a steam-bath. The resultant clear solution was cooled in ice, whereupon a viscous oil separated. The supernatant liquid was decanted, the oil dissolved in hot water, and the solution basified. The yellow precipitate of 2 : 6-*bisdiethylaminoanthracene* (II; R = Et) was filtered off, dried and recrystallised from ethanol; it had m. p. 131·5—133·5° (0·25 g., 55%). For analysis the anthracene was recrystallised from ethanol containing a little benzene (lemon-yellow needles, m. p. 133·5—134·5°) (Found: C, 82·3; H, 9·0; N, 8·95. $C_{22}H_{28}N_2$ requires C, 82·5; H, 8·8; N, 8·75%). Solutions of the anthracene showed a strong blue fluorescence.

(*b*) The reaction mixture from *p*-dimethylaminobenzaldehyde (5·0 g.) was set aside for 2 days by which time an appreciable precipitate of the tin complex of 2 : 6-bisdimethylaminoanthracene (II; R = Me) had separated. The filtered solution was worked up as described for the diethylamino-analogue to yield 2 : 6-*bisdimethylamino*-9 : 10-*dihydro*-9 : 10-*dihydroxyanthracene* (VII; R = Me) as white needles (after several recrystallisations from benzene), m. p. 154—155° (decomp.) (0·8 g., 16%) (Found: C, 72·3; H, 7·3; N, 9·4. $C_{18}H_{22}O_2N_2$ requires C, 72·5; H, 7·4; N, 9·4%).

The diol (VII; R = Me) (0·1 g.), treated with a solution of tin (0·4 g.) in hydrochloric acid (6·0 ml.; 1 : 1 v/v) as described for the diethylamino-analogue (VII; R = Et), yielded 2 : 6-bisdimethylaminoanthracene (II; R = Me) which, recrystallised from benzene, had m. p. 253—254° (alone and mixed) (0·067 g., 76%).

Action of Hydrochloric Acid on 2 : 6-*Bisdiethylamino*-9 : 10-*dihydro*-9 : 10-*dihydroxyanthracene*.—A solution of the diol (VII; R = Et) (1·0 g.) in hydrochloric acid (16 ml., 1 : 1 v/v) was refluxed for 2 hr. On dilution with water a deep pink colour developed which disappeared later. The solution was basified and the precipitated yellow oil extracted with benzene and ether. The dried extracts were evaporated, and the residue was treated with a little warm ethanol, whereupon a small amount of a white crystalline solid separated. This *substance*, twice recrystallised from ethanolic benzene, had m. p. 243—244° (Found: C, 78·4; H, 8·7; N, 8·1. $C_{22}H_{28}ON_2$ requires C, 78·5; H, 8·4; N, 8·3%).

The ethanol solution was evaporated *in vacuo*, and the residue taken up in benzene and chromatographed on an alumina column (1 × 10 cm.). Development with benzene produced a colourless region which fluoresced strongly in ultraviolet light, followed by a broad yellow band. The fluorescent region was washed through and the solvent removed to yield 2 : 6-bisdiethylaminoanthracene (II; R = Et); recrystallised from ethanol–benzene and sublimed, this had m. p. 130—131° (alone and mixed) (10 mg., 1·0%); it was accompanied by a trace of the above white substance, m. p. 240—242° (from ethanol–benzene).

The yellow region of the column was removed and eluted with ethanol. Evaporation of the solvent yielded 2 : 6-*bisdiethylaminoanthrone* (XII) which was purified by recrystallisation from light petroleum (b. p. 60—80°) containing a little ethanol, then having m. p. 95·5—96·5° (0·31 g., 30%). For analysis it was recrystallised several times from the same solvent mixture (m. p. 97·5—98·5°) (Found: C, 78·15; H, 8·6; N, 8·3. $C_{22}H_{28}ON_2$ requires C, 78·5; H, 8·4; N, 8·3%).

The anthrone-containing band was followed by a pinkish region which gave a yellow oil on elution with ethanol and evaporation. The oil, which failed to crystallise, rapidly became green in air.

Action of Oxidising Agents on 2 : 6-*Bisdialkylaminoanthracenes*.—Dilute acidic solutions of the anthracenes became deep red when treated with bromine water, sodium hypochlorite, potassium ferricyanide, ferric chloride, potassium dichromate, or warm hydrogen peroxide. The last reagent was found to be most convenient for studying the effect. The following simple test procedure was adopted for comparison of the behaviour of the different anthracenes. To each of the anthracenes to be compared (0·5—1·0 mg.), contained in separate test tubes, hydrochloric acid (1·0 ml., 1 : 1 v/v) and hydrogen peroxide (0·5 ml.; 0·3%) were added. The tubes were then placed in boiling water and the colour reactions observed. Under these conditions the colour from 2 : 6 bisdimethylamino- (II; R = Me) and 2 : 6-bisdiethylamino-anthracene (II;

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R = Et) was discharged in 1—2 min., the colour from the latter being much less intense. Benzo(1 : 2-7′ : 8′)-(4 : 5-7″ : 8″)dijulolidine (VI) gave an extremely intense colour which was not completely discharged after 60 min. at 100°.

In each case the permanence of the colour was enhanced by dilution and by increased acid concentration.

Oxidation of Benzo(1 : 2-7′ : 8′)(4 : 5-7″ : 8″)*dijulolidine* (VI).—The compound (VI) (0·2 g.) was triturated with concentrated hydrochloric acid (0·5 ml.) and water (1·5 ml.). 30% Hydrogen peroxide (0·35 ml.) was added and the mixture warmed gently with vigorous stirring. The *dichloride* of the cation (XV) separated as blue needles of the tetrahydrate, which were filtered off and dried for 2—3 hr. over potassium hydroxide *in vacuo* and then at atmospheric pressure over silica gel (yield 0·23 g., 85%) (Found: C, 60·8; H, 6·85. $C_{26}H_{28}N_2Cl_2,4H_2O$ requires C, 61·0; H, 7·0%).

The chloride was very soluble in water giving an intensely red solution having an absorption maximum at 516 mμ. It was decomposed on exposure to light or on prolonged storage *in vacuo*. An aqueous solution of the chloride (0·1 g.) was decolorised immediately on addition of alkali with deposition of an oil which yielded the anthracene derivative (VI), m. p. 226—228° (decomp.) (from ethanol–benzene) (0·07 g., 42%).

The *dipicrate*, prepared in aqueous solution, was a sparingly soluble, dark brown powder (Found: C, 55·3; H, 4·3. $C_{38}H_{32}O_{14}N_8$ requires C, 55·3; H, 3·9%). The *chloroplatinate* was an insoluble brown powder (Found: C, 40·1; H, 3·75; residue, 22. $C_{26}H_{28}N_2Cl_6Pt$ requires C, 40·2; H, 3·65; Pt, 25·0%). The *perchlorate* was a moderately soluble brown-black powder which exploded when heated (Found: C, 55·4; H, 5·3. $C_{26}H_{28}O_8N_2Cl_2$ requires C, 55·0; H, 5·0%).

An aqueous solution of the chloride (0·15 g.) was treated dropwise with 30% titanous

Infrared absorption bands (*cm.*$^{-1}$) *of anthracene derivatives.*

(*a*) 2 : 6-Bisdimethylamino- (II; R = Me), (*b*) 2 : 6-bisdiethylamino- (II; R = Et), (*c*) 2 : 6-bisethylmethylamino-anthracene, (*d*) benzo(1 : 2-7′ : 8′)(4 : 5-7″ : 8″)dijulolidine (VI), (*e*) 2 : 6-bisdiethylaminoanthrone (XII), (*f*) substance $C_{22}H_{28}ON_2$, (*g*) 2 : 6-bisdiethylamino-9 : 10-dihydro-9 : 10-dihydroxyanthracene (VII; R = Et), (*h*) 2 : 6-bisdimethylamino-9 : 10-dihydro-9 : 10-dihydroxyanthracene (VII; R = Me).

(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*f*)	(*g*)	(*h*)
818 s	812 s	820 s	—	823 m	804 s	805 s	809 s
—	—	—	866 w	851 w	858 w	—	—
—	—	895 w	892 w	—	—	—	—
—	—	—	—	929 w	920 w	—	—
950 m	—	945 w	953 s	—	—	—	941 m
964 m	961 m	965 m	—	—	—	—	—
—	—	986 m	—	985 m	—	—	—
1005 w	1008 w	1006 w	—	1013 m	1007 m	1005 m	1010 m
1021 w	1019 w	—	1034 w	—	1036 s	1022 s	1037 s
—	—	—	1054 w	—	—	1049 m	1061 m
1070 m	1081 m	1084 m	1078 m	1080 m	1080 m	1078 m	—
—	1095 w	1110 m	—	1096 m	1098 w	1100 w	—
—	—	—	—	1131 w	—	1125 w	1137 s
1171 m	1158 m	1161 s	1161 s	1161 s	1160 m	1152 s	1170 s
1189 s	1191 s	1190 s	1189 s	1190 s	1196 m	1186 s	1188 m
—	1205 m	1215 m	1211 m	1201 m	1203 m	1203 m	1209 m
1229 m	1230 w	—	—	—	—	—	—
1241 w	—	—	1245 w	1250 s	—	—	—
1283 w	1280 s	1274 s	—	1278 s	1270 s	1270 s	1280 w
—	—	—	1311 s	—	—	—	—
—	—	1320 w	—	1338 m	1324 w	—	1325 s
1364 s	1360 s	1350 s	1345 m	1362 s	1359 s	1351 s	—
—	1405 m	—	—	1408 s	1406 m	1398 m	—
1525 s	1530 s	1522 s	1500 s	1529 s	1530 s	1520 s	1524 s
1557 w	1558 w	1560 w	—	1556 m	1567 w	1567 w	1575 w
—	—	—	—	1597 s	—	—	—
1608 s	1610 s	1606 s	1603 m	1615 s	1615 s	1609 s	1615 s
—	—	—	—	1670 s	—	—	—
—	—	—	—	—	—	—	3340 b
—	—	—	—	—	—	3450 b	—
—	—	—	—	—	—	3505b	—

s = strong; m = medium; w = weak; b = broad.

chloride solution until the colour was completely discharged. The precipitated crude hydrochloride of (VI) was filtered off, and the anthracene liberated by alkali. Recrystallised from ethanolic benzene, it had m. p. 224—226° (alone and mixed) (0·03 g., 30%).

Infrared Spectra.—The spectra were determined in Nujol. The Table records the more important bands of the various 2 : 6-bisdialkylaminoanthracene derivatives prepared.

The author is indebted to the University of Manchester for an I.C.I. Research Fellowship.

THE UNIVERSITY, MANCHESTER. [*Received, August 8th*, 1956.]

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201. *The Dipole Moment of the Helium Hydride Molecule-ion*, HeH^{2+}.

By B. F. GRAY and H. O. PRITCHARD.

The dipole moment of the ground-state of the HeH^{2+} molecule-ion has been calculated for internuclear separations up to $5a_0$ (atomic units) from the known exact wave functions for the system.

IT has not previously been possible to calculate exactly the dipole moment of any heteronuclear molecular system, but Bates and Carson [1] have recently published the exact wave functions for a number of states of the HeH^{2+} ion. Of the wave functions given, only that for the ground-state ($1s\sigma$) resembles what one generally envisages a normal bonding molecular orbital to look like, and since this system bears the same relation to heteronuclear diatomic molecules as does H_2^+ to homonuclear systems, a knowledge of the variation of dipole moment with distance is of particular interest.

The wave function is written in the form

$$\Psi(\phi, \lambda, \mu) = \Phi(\phi)\,\Lambda(\lambda)\,\mathrm{M}(\mu)$$

where ϕ, λ, and μ are the usual confocal elliptical co-ordinates. The separate parts of the wave function are

$$\Phi(\phi) = \cos m\phi$$

$$\Lambda(\lambda) = (\lambda^2 - 1)^{\frac{1}{2}m}(\lambda + 1)^{\sigma} e^{-p\lambda} \sum_{s=0}^{\infty} g_s \left(\frac{\lambda - 1}{\lambda + 1}\right)^s$$

and

$$\mathrm{M}(\mu) = e^{-p\mu} \sum_{t=m}^{\infty} f_t' \mathrm{P}_t^m(\mu)$$

where m is the orbital angular momentum quantum number and $\mathrm{P}_t^m(\mu)$ is the associated Legendre polynomial. Bates and Carson give values of the parameters σ, p, g_s, and f_t' (not normalised) for a series of thirteen internuclear separations R in the range $0 \leqslant R \leqslant 5a_0$. The normalising constant N may be determined from the expression

$$\int \Psi^2 d\tau = N^2 \frac{R^3}{8} \int_0^{2\pi} \int_1^{\infty} \int_{-1}^{+1} \Psi^2 \Lambda^2 \mathrm{M}^2 (\lambda^2 - \mu^2) d\mu d\lambda d\phi = 1$$

and the average distance of the electron from the He^{2+} nucleus (taken as the origin of x) is

$$\int \Psi x \Psi d\tau = N^2 \frac{R^4}{16} \int_0^{2\pi} \int_1^{\infty} \int_{-1}^{+1} \Phi^2 \Lambda^2 \mathrm{M}^2 (\lambda^3\mu + \lambda^2 - \lambda\mu^2 - \mu^2) d\mu d\lambda d\phi$$

Integration over the angle ϕ leads simply to a multiplying factor of 2π, and there remain the integrals of Λ^2, $\lambda\Lambda^2$, $\lambda^2\Lambda^2$, $\lambda^3\Lambda^2$ over the range $1 \leqslant \lambda \leqslant \infty$ and of M^2, $\mu\mathrm{M}^2$, $\mu^2\mathrm{M}^2$, $\mu^3\mathrm{M}^2$ over the range $-1 \leqslant \mu \leqslant 1$, which were evaluated numerically by using the Manchester University

[1] Bates and Carson, *Proc. Roy. Soc.*, 1956, *A*, **234**, 207.

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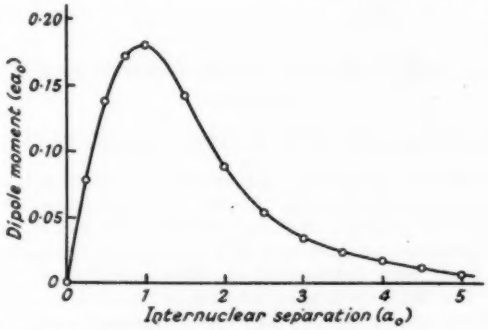
Computer. The M integrals were readily obtained by using a 16-point Gaussian quadrature. The Λ integrals were transformed into the form

$$\int_0^\infty e^{-t} f(t)\, dt$$

and were then evaluated by using a modified Lagrangian quadrature [2] to a high degree of precision (for the distance $R = 1$, the 7-point and 10-point calculations gave answers differing by 3 or less in the eighth decimal place, and so the 10-point quadrature was used throughout).

The results are given in the Table in the form of the directly calculated function $2\pi R^3N^2/8$ (from which N can be found) and the derived value of the dipole moment of the system. Care has to be taken in defining the dipole moment in a charged system (*e.g.* the separation of the



positive and negative electrical centres tends to ∞ as $R \longrightarrow \infty$) but where the number of electrons is equal to the difference in charge between the two nuclei, the dipole moment is given simply by $\int \Psi x \Psi d\tau$. This is obtained by reducing each positive charge by one unit (*i.e.* in the general case by subtracting non-polar charge distributions until an equal number of positive and negative charges are left) thereby leaving a neutral system consisting of a single positive charge at the origin with an electron at an average distance $\int \Psi x \Psi d\tau$ away from it.

R (a_0)	$2\pi R^3N^2/8$	$\int \Psi x \Psi d\tau$ (ea_0)	R (a_0)	$2\pi R^3N^2/8$	$\int \Psi x \Psi d\tau$ (ea_0)	R (a_0)	$2\pi R^3N^2/8$	$\int \Psi x \Psi d\tau$ (ea_0)
0	—	0	1·5	17·198	0·1419	3·5	206·2	0·0246
0·25	0·088306	0·0783	2·0	41·01	0·0885	4·0	302·1	0·0182
0·50	0·62969	0·1373	2·5	78·65	0·0535	4·5	423·5	0·0142
0·75	2·0564	0·1713	3·0	132·7	0·0347	5·0	573·4	0·0114
1·0	4·9123	0·1797						

The variation of dipole moment with distance takes almost the expected form [3] and is shown in the Figure. It is unfortunate that the HeH^{2+} molecule is not a stable system and there may be a case from a spectroscopic point of view for repeating the whole calculation for a hypothetical molecule consisting of an electron in the field of two centres of charges $+\frac{1}{2}$ and $+1$, to see where the maximum in the dipole moment lies in relation to the minimum in the potential energy.

There is, however, an unexpectedly large disparity between the dipole moment calculated here and the value given by the L.C.A.O. approximation. At $R = 1{\cdot}5a_0$ a simple linear combination of H(1s) and He(1s) functions (with variation of Z) gives an energy which is only about $\frac{1}{2}\%$ in error (cf. Coulson and Duncanson [4] and Bates and Carson [1]), but the corresponding dipole moment is only about $0{\cdot}019ea_0$ as opposed to about $0{\cdot}14ea_0$ given by the exact calculation.

[2] Salzer and Zucker, *Bull. Amer. Math. Soc.*, 1949, **55**, 1004.
[3] Herzberg, " Spectra of Diatomic Molecules," D. Van Nostrand, New York, 1950, p. 97.
[4] Duncanson and Coulson, *Proc. Roy. Soc.*, 1938, *A*, **165**, 90.

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Note.—Since this paper was written, Moiseiwitsch and Stewart [5] have given exact dipole moments for six of the internuclear distances; their values agree exactly with ours. They also compare the exact values with some obtained from orbital approximations; it is clear from both sets of calculations that quite an accurate representation of the energy gives no guarantee that the wave function will lead to a dipole moment which is even of the correct order of magnitude.

We thank the staff of the Manchester University Computing Machine Laboratory for the use of their facilities, and D.S.I.R. for a maintenance grant (to B. F. G.).

MANCHESTER UNIVERSITY. [*Received, August 24th,* 1956.]

[5] Moiseiwitsch and Stewart, *Proc. Phys. Soc.*, 1956, *A*, **69**, 480.

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202. *Niobium and Tantalum Pentachlorides and Their Binary System.*

By J. B. AINSCOUGH, R. J. W. HOLT, and F. W. TROWSE.

The boiling points of niobium and tantalum pentachlorides have been measured over a range of pressures. At 760 mm. pressure they were found to be 247·4° ± 0·1° and 232·9° ± 0·1° respectively, and the heats of vaporisation were calculated as 12·6 and 13·1 kcal. mole^{-1} respectively. The triple points have been determined as 203·4° ± 0·2° and 215·9° ± 0·1° respectively. The liquid–vapour equilibrium in the system niobium pentachloride–tantalum pentachloride has been examined and the relative volatility ($TaCl_5$: $NbCl_5$) at atmospheric pressure found to be 1·36 over the whole range of mixture compositions.

PREVIOUS investigations of the vapour pressure of niobium pentachloride, all of which gave different boiling points, have been reported.[1,2,3] Schäfer, Bayer, and Lehmann[4] combined the published vapour-pressure data with a measurement of the melting point made by Schäfer and Pietruck,[5] and obtained a boiling point of 250° for niobium pentachloride.

The relative volatilities of the pentachlorides have been studied theoretically by Geldart and Steele.[6]

EXPERIMENTAL

The halides were prepared by direct chlorination of the metals at 450° by use of chlorine which had been dried by bubbling through sulphuric acid. Oxide, present as an impurity in the metals, led to the formation of oxychloride, the amount of which could be greatly reduced by adding carbon tetrachloride to the pentachloride whilst it was gently refluxed under an air condenser, and then pumping off volatile products after cooling. The pentachlorides were purified by fractional distillation through a 60-cm. electrically-heated column packed with glass Fenske helices. A magnetically-operated swinging funnel was used to deliver about 1/50th of the total reflux to the receiver. One of the fractions of niobium pentachloride was further purified by vacuum sublimation at 100°, the pentachloride subliming much more rapidly than the oxychloride: at 190° no separation was possible. This material was used for the boiling-point and triple-point determinations (Found: Ta, 50·2 ± 0·5; Nb, 0·19. Calc. for $TaCl_5$: Ta, 50·50) (Found: Nb, 34·7 ± 0·3; Ta, 0·015. Calc. for $NbCl_5$: Nb, 34·38%).

[1] Opichtina and Fleischer, *Zhur. Obshchei. Khim.*, 1937, **7**, 2016.
[2] Tarasenkow and Komandin, *ibid.*, 1940, **10**, 1319.
[3] Alexander and Fairbrother, *J.*, 1949, S223.
[4] Schäfer, Bayer, and Lehmann, *Z. anorg. Chem.*, 1952, **268**, 268.
[5] Schäfer and Pietruck, *ibid.*, 1951, **267**, 174.
[6] Geldart and Steele, Paper No. 16, Presented at an Institution of Mining and Metallurgy Symposium, March, 1956.

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Attempts to prepare the white modification of niobium pentachloride described by Alexander and Fairbrother [3] were unsuccessful. A white material, similar in appearance to that obtained by us by burning niobium trichloride in oxygen, was sometimes found with the unsublimed but never with the sublimed pentachloride and could always be explained as niobium oxychloride present as impurity.

Boiling-point Apparatus.—Boiling points were taken in a glass tube, electrically heated at the bottom and lagged over the lower 10 cm. of its length. It was connected to a manometer and a pressure regulating system in which fluctuations were damped to ±2 mm. by a 750 ml. flask. To obtain pressures above atmospheric, dry nitrogen was blown into the apparatus and allowed to escape through a mercury bubbler, the head of mercury thus determining the excess

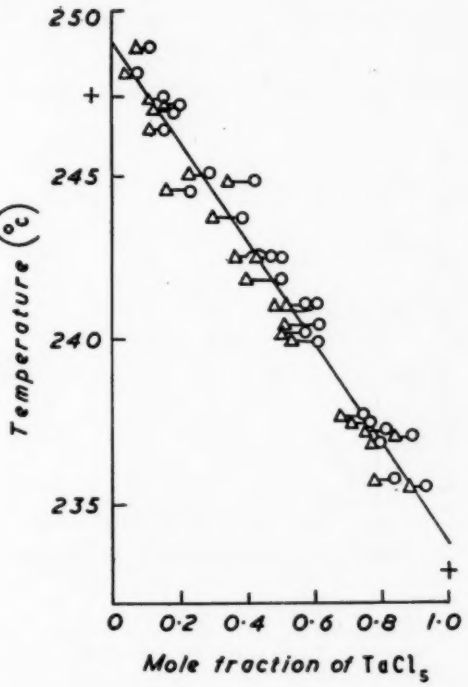

FIG. 1. *Liquid–vapour equilibrium for the niobium pentachloride–tantalum pentachloride system.*

△ liquid phase, ○ vapour phase, + boiling points of the pure components.

of pressure. Pressures below atmospheric were obtained by slowly evacuating the apparatus and admitting dry air through the bubbler.

About 60 g. of pentachloride were distilled into the apparatus which was evacuated and then filled with dry nitrogen. The charge was melted and the heater adjusted so that refluxing took place just above the lagging. A calibrated bare thermocouple (Pt/Pt–13% Rh), so arranged that the junction could not be cooled by condensate running down the leads, was used to measure temperature. The thermocouple E.M.F. was measured on a millivolt potentiometer which could be read to the nearest microvolt, corresponding to 0·1° at 200°. The thermocouple junction was usually placed in the vapour, though some of the measurements with tantalum pentachloride were made with it in the liquid. Pressure and temperature readings were taken and when three consecutive temperature readings at 5-min. intervals, at the same pressure, agreed within 0·1° they were taken as the boiling point at that pressure.

Triple-point Apparatus.—The triple point was measured by plotting the cooling curve of the liquid, under its own vapour, in a glass bulb fitted with a bare thermocouple. After introduction of about 60 g. of pentachloride the bulb was evacuated and sealed off. The charge was melted with a flame and the bulb placed in an electrically heated Dewar vessel and covered with asbestos wool. When the temperature in the bulb reached about 240° the heater was switched

off and temperature readings taken, at intervals of about 1 min., from which the cooling curve was drawn.

The Equilibrium Still.—The still was of a recirculating type, based on that described by Othmer.[7] It was charged with a mixture of the pentachlorides and set up in an oven maintained at about 230°. The still heater was adjusted to give continuous boiling, the pressure adjusted to 760 mm., and the temperature measured at regular intervals. Equilibrium was assumed to have been attained when the boiling point was constant to 0·1° over a period of 20 min. The vapour sample present as condensate in a U-tube was collected by solidification by rapidly cooling the tube with a jet of air, and the liquid sample was taken in a side arm on the boiler in the same way. Care was taken, when collecting the liquid sample, that the initial solidification occurred close to the boiler, thus minimising the effects of any change of composition during solidification. The sample tubes were drawn off under vacuum and their contents analysed for niobium and tantalum.

Results.—Fourteen measurements of the boiling point of niobium pentachloride were made at pressures between 680 and 900 mm. Over this range the b. p. can be related to the pressure

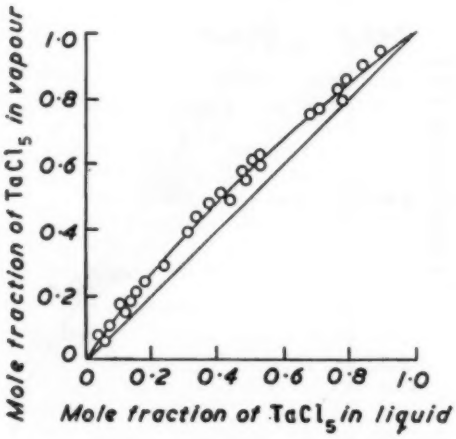

FIG. 2. *Liquid–vapour equilibrium for the niobium pentachloride–tantalum pentachloride system.*

by the equation $\log p$ (mm.) $= 8{\cdot}201 - 2{\cdot}770 \times 10^3/T$, which corresponds to b. p. 247·4° ± 0·1° at 760 mm. The greatest deviation of any point from this line corresponds to an error of $2{\cdot}5 \times 10^{-3}$ in $\log p$.

Nineteen measurements of the boiling point of tantalum pentachloride were made with the thermocouple in the vapour over the same pressure range. These measurements fit the equation $\log p$ (mm.) $= 8{\cdot}543 - 2{\cdot}865 \times 10^3/T$, giving b. p. at 760 mm. pressure of 232·9° ± 0·1°. The maximum deviation of any point from this line corresponds to an error of 3×10^{-3} in $\log p$. Other measurements with the thermocouple in the liquid, though self-consistent, were about 1° higher than those measured in the vapour: this was probably due to superheating. From the vapour-pressure equations, which were obtained by the method of least squares, the heats and entropies of vaporisation (ΔH_v and ΔS_v) were calculated.

Cooling curves were drawn for each of the pentachlorides. Projection of the plateaux of these curves back to the portions representing cooling of the liquids gives the triple point of tantalum pentachloride as 215·9° ± 0·1°, and of niobium pentachloride as 203·4° ± 0·2° (203·0° ± 0·2° before sublimation).

The mole fractions of the components in the binary mixture were calculated from the results of the analyses of the liquid and vapour samples from the equilibrium still, and their values normalised so that the sum for any sample was unity. The sum calculated directly from the analytical figures always lay between 0·97 and 1·04. Results are shown in the Figures. The

[7] Othmer, *Ind. Eng. Chem.*, 1928, **20**, 743.

relative volatility appeared to be constant over the whole range of mixture compositions and a mean value of 1·36 was calculated from the experimental values lying between 1·20 and 1·48 (two values below 1·1 being rejected). The probable error in a single observation was 0·04.

Discussion

Phase Relations of the Pure Compounds.—A comparison between this and other published work is shown in the Table. The boiling and triple points reported here are 4—6° lower than those obtained by Alexander and Fairbrother [3] but the triple points are only

	Niobium pentachloride			Tantalum pentachloride		
	Present work	Alexander and Fairbrother	Schäfer *et al.*	Present work	Alexander and Fairbrother	Schäfer *et al.*
Boiling point °	247·4 ± 0·1	254·0 ± 0·1	250	232·9 ± 0·1	239·3 ± 0·1	—
Triple point °	203·4 ± 0·2	209·5 ± 0·5	204·7	215·0 ± 0·1	220·0 ± 0·5	216·5
ΔH_s (kcal. mole^{-1}) ...	12·6 ± 0·1	13·2	13·1	13·1 ± 0·4	13·6	—
ΔS_s (cal. deg.$^{-1}$ mole^{-1})	24·3 ± 0·3	—	25·1	25·9 ± 1·3	—	—

1° lower than values given by Schäfer *et al.*[4, 5] Examination of Alexander and Fairbrother's work permits a possible explanation of these discrepancies, in that their pentachlorides may have been contaminated with oxychlorides. The present work has shown that at 200°, the temperature used by Alexander and Fairbrother,[8] it is not possible to separate niobium oxychloride and pentachloride by vacuum sublimation and any oxide in the original metal would be carried through the purification as oxychloride.

The Binary System.—It can be seen that there is a considerable scatter of points in Fig. 1, whereas in Fig. 2 the scatter is much less, suggesting that most of the errors must have been in the measured temperatures. The calculated boiling points of the pure components are also shown in Fig. 1 and all the temperature measurements lie above the line joining these points. It is probable that, in spite of the treatment with carbon tetrachloride, there was contamination by oxychloride which raised the b. p. The mean value of the relative volatility is 1·36: if mixtures of the pentachlorides behaved ideally the relative volatility would be 1·42 and 1·44 at the tantalum and niobium ends of the range respectively.

We thank the Chemical Services Department, Springfields Works, for carrying out the analyses, and the Director of Research and Development of this Group for permission to publish this paper.

Research and Development Branch,
United Kingdom Atomic Energy Authority, Industrial Group,
Springfields Works, Preston, Lancs. [*Received, September 14th*, 1956.]

[8] Fairbrother, personal communication.

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203. *Polyfluoroalkyl Compounds of Silicon. Part II.* Free-radical Reaction of Dialkylsilanes with Fluoro-olefins.†*

By A. M. Geyer and R. N. Haszeldine.

A dialkylsilane R_2SiH_2 reacts with tetrafluoroethylene to give

$$R_2SiH{\cdot}[CF_2{\cdot}CF_2]_n{\cdot}H$$

Secondary reactions produce compounds of the type

$$H{\cdot}[CF_2{\cdot}CF_2]_x{\cdot}SiR_2{\cdot}[CF_2{\cdot}CF_2]_y{\cdot}H$$

Radical-chain mechanisms are proposed for these reactions. The value of n is determined by the reactant ratio, and yields of $Me_2SiH(CF_2{\cdot}CF_2H)$ as high as 83% have been obtained from dimethylsilane. The SiH bond is reactive and further reaction with tetrafluoroethylene gives $Me_2Si(CF_2{\cdot}CF_2H)_2$. The polyfluoroalkyl silicon compounds are stable to water but with aqueous alkali liberate the polyfluoroalkyl group quantitatively as $H{\cdot}[CF_2{\cdot}CF_2]_n{\cdot}H$. Variations in the Si–H infrared frequency are discussed.

A CLEAR idea of the reactivity and reactions of the $SiCl_3$ radical derived from trichlorosilane [1] can be gained from the study [2] of perfluoroalkyl radicals such as CF_3, and the convenient synthesis of compounds $H{\cdot}[CF_2{\cdot}CF_2]_n{\cdot}SiCl_3$ by reaction of trichlorosilane with tetrafluoroethylene was thus clearly predictable. Much less predictable, however, are the properties and reactivities of inorganic radicals derived from silanes such as $CH_3{\cdot}SiH_3$, $(CH_3)_2SiH_2$, or SiH_4 or in general $RSiH_3$, R_2SiH_2 (R = H, alkyl, aryl, etc.), containing more than one hydrogen atom linked directly to silicon. We now record the beginning of a general investigation [3] of the reaction of free radicals derived from inorganic covalent hydrides with olefins which are sensitive to free-radical attack, *e.g.*, fluoro-olefins, and, specifically, the reaction of dimethylsilane with tetrafluoroethylene.

Dimethylsilane and tetrafluoroethylene fail to react in the dark even during four months. Exposure to light of wavelength <3000 Å initiates an extremely rapid chain reaction; liquid products, formed in the vapour phase as a mist, appear immediately and the reaction, which is soon complete, is thus considerably faster than the corresponding reaction of trichlorosilane described in Part I. The products are all of the types (I)—(III). Hydrogen is not detectable, and all of the tetrafluoroethylene is consumed. The reaction can be effected with equal facility at room temperature in sealed silica tubes at super-atmospheric pressure, or in the apparatus described earlier [4] for photochemical reactions on approximately 1 molar scale at less than atmospheric pressure.

The main factor influencing the ratio of the products (I), (II), and (III) is the mole-ratio of dimethylsilane to tetrafluoroethylene used, and this reveals the facility of the chain-transfer step in the radical-chain reaction :

$$(CH_3)_2SiH_2 \xrightarrow{h\nu} (CH_3)_2\dot{S}iH + H\cdot$$

$$(CH_3)_2\dot{S}iH + C_2F_4 \longrightarrow (CH_3)_2Si(H)(CF_2{\cdot}CF_2\cdot) \quad \text{. . . . Initiation}$$

$$(CH_3)_2Si(H)(CF_2{\cdot}CF_2\cdot) + C_2F_4 \longrightarrow (CH_3)_2Si(H)([CF_2{\cdot}CF_2]_n\cdot) \quad \text{. . . Propagation}$$

$$(CH_3)_2Si(H)([CF_2{\cdot}CF_2]_n\cdot) + (CH_3)_2SiH_2 \longrightarrow (CH_3)_2Si(H)([CF_2{\cdot}CF_2]_n{\cdot}H) + (CH_3)_2\dot{S}iH$$

$$\longrightarrow \text{etc.} \quad \text{. . . Chain transfer}$$

* Part I, *J.*, 1956, 962.

† For a preliminary communication see *Nature*, 1956, **178**, 808.

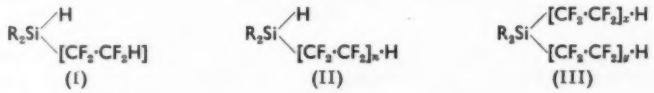
[1] Haszeldine and Marklow, *J.*, 1956, 962.

[2] *E.g.*, see Haszeldine and Osborne, *J.*, 1956, 61, and preceding papers.

[3] Geyer and Haszeldine, *Nature*, 1956, **178**, 808.

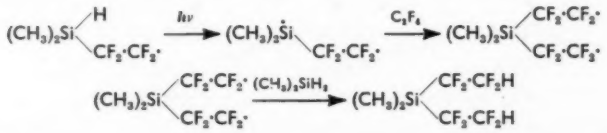
[4] Barr and Haszeldine, *J.*, 1955, 1881.

Use of a 5 : 1 ratio of dimethylsilane to tetrafluoroethylene gives the compounds (I; R = Me), (II; R = Me, $n = 2$), and (III; R = Me, $x = y = 1$) in 83, 7, and 2% yield respectively. The main reaction involved in the formation of compounds containing more than



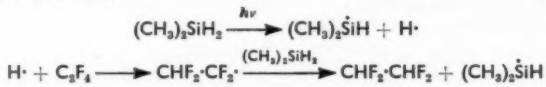
(I) (II) (III)

one C_2F_4 unit per silicon atom is thus the chain-propagation mentioned above rather than the formation of mixed silyl alkyl diradicals; *e. g.*,



The compound (III; R = Me, $x = y = 1$) is formed by the further reaction of (I; R = Me) with tetrafluoroethylene as described below. The predominance of the propagation step with tetrafluoroethylene again illustrates the ease of free-radical polymerisation of this olefin and the necessity for a highly efficient chain-transfer agent if the chain length of the polymer is to be controlled.[5]

The absence of even traces of hydrogen from the reaction products suggests [1,6] that attack by hydrogen atoms on the olefin occurs to give a polyfluoroalkyl radical which generates a dimethylsilyl radical from dimethylsilane and is thereby converted into 1 : 1 : 2 : 2-tetrafluoroethane :



A dimethylsilane : tetrafluoroethylene ratio of *ca.* 1·5 : 1 gives dimethyl-(1 : 1 : 2 : 2-tetrafluoroethyl)silane (I; R = Me) in *ca.* 50% yield, and the amount of product containing more than one C_2F_4 unit per silicon atom is correspondingly increased. The material containing two C_2F_4 units per silicon atom is an isomeric mixture of dimethyl-(1 : 1 : 2 : 2 : 3 : 3 : 4 : 4-octafluorobutyl)silane (II; R = Me, $n = 2$) formed in 20% yield, and dimethyldi-(1 : 1 : 2 : 2-tetrafluoroethyl)silane (III; R = Me, $x = y = 1$) formed in 7% yield. The material containing three C_2F_4 units per silicon atom is similarly an isomeric mixture of (1 : 1 : 2 : 2 : 3 : 3 : 4 : 4 : 5 : 5 : 6 : 6-dodecafluorohexyl)dimethylsilane (II; R = Me, $n = 3$) and dimethyl-(1 : 1 : 2 : 2 : 3 : 3 : 4 : 4-octafluorobutyl)-(1 : 1 : 2 : 2-tetrafluoroethyl)silane (III; R = Me, $x = 1$, $y = 2$) formed in 0·5 and 8% yields respectively. Material of even higher molecular weight is also present. These products arise by a primary initiation, propagation, and chain-transfer as outlined above, followed by secondary reactions of the products which contain Si–H bonds with tetrafluoroethylene as shown in the scheme on page 1040.

The primary reaction, considered to be that shown on the main line of the scheme, yields a series of products of type (II; R = Me, $n = 1, 2, 3 \ldots$ etc.) each containing an Si–H bond, with the value of n governed mainly by reactant ratio. As the concentration of the compound (I; R = Me) increases it eventually becomes comparable with that of the unconsumed dimethylsilane present at that time, and the secondary reaction of (I; R = Me) with tetrafluoroethylene becomes increasingly important; the relative amounts of the compounds (III; R = Me, $x = 1$, $y = 1, 2, 3 \ldots$ etc.) produced by

[5] Haszeldine, *J.*, 1953, 3761; 1955, 4291.
[6] Haszeldine and Steele, *J.*, 1954, 3747.

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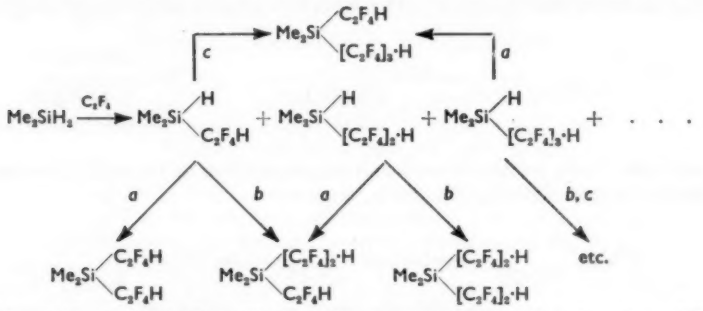
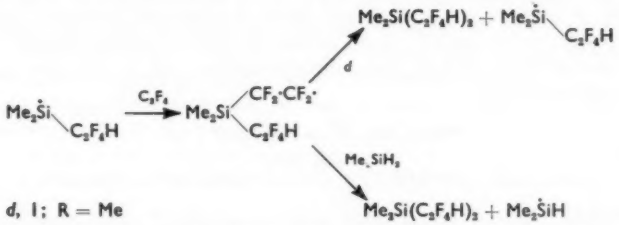
this secondary reaction at any given time will vary throughout the reaction, since the concentration of dimethylsilane and of (I; R = Me) will be changing. It should also



[a] Chain reaction with tetrafluoroethylene with absence of propagation step; *i.e.*, addition of one C_2F_4 unit.
[b] Chain reaction with tetrafluoroethylene with addition of two C_2F_4 units at propagation step.
[c] Chain reaction with tetrafluoroethylene with addition of three C_2F_4 units at propagation step.

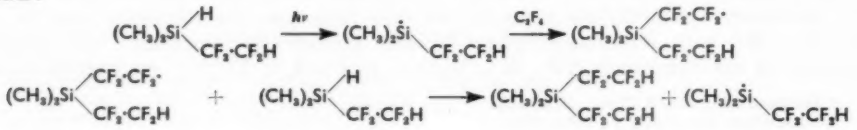
be noted that the chain-transfer step in this secondary reaction occurring at a stage when an appreciable amount of dimethylsilane is present can occur by generation of dimethylsilyl radicals as well as of dimethyl-(1 : 1 : 2 : 2-tetrafluoroethyl)silyl radicals :



d, I; R = Me

and this will tend to produce mainly (III; R = Me, $x = y = 1$) from (I; R = Me). As the concentration of dimethylsilane decreases further, *i.e.*, towards the end of the primary reaction, the propagation reaction with (I; R = Me) will increase in importance. The secondary reaction of (II; R = Me, $n = 2$) with tetrafluoroethylene will also occur about this stage as the concentration of the former becomes comparable with that of dimethylsilane and (I; R = Me). The final yields of the products indicate that in the *primary* reaction the chain propagation initially gives (II; R = Me, $n = 2$) in 20—30% yield and (I; R = Me) in 50—60% yield; these yields are then reduced by the occurrence of the secondary reactions. The fact that the compounds (III; R = Me, $x = y = 1$) and (III; R = Me, $x = 1$, $y = 2$) are formed in approximately equal yields (8%) suggests that in each of the secondary reactions the main product is that resulting from addition of one C_2F_4 unit in *ca.* 50% yield and of two C_2F_4 units in *ca.* 25% yield just as in the primary reaction.

That compounds of type (II; R = Me, $n = 1, 2, 3 \ldots$) can react further with tetrafluoroethylene was shown by the reaction of dimethyl-(1 : 1 : 2 : 2-tetrafluoroethyl)silane with tetrafluoroethylene to give dimethyldi-(1 : 1 : 2 : 2-tetrafluoroethyl)silane in 90% yield :



A stepwise procedure of this type enables compounds free from isomers to be obtained, and also enables a different alkyl group to be attached to silicon if required :

$$R_2SiH_2 \xrightarrow{R_2'C:CR_2'} R_2SiH\cdot[CR_2'\cdot CR_2']\cdot H \xrightarrow{R_2''C:CR_2''} R_2Si\begin{cases}[CR_2''\cdot CR_2'']\cdot H\\ [CR_2'\cdot CR_2']\cdot H\end{cases}$$

When the ratio dialkylsilane : tetrafluoroethylene is very small, the silane acts merely as an initiator for the long-chain polymerisation of tetrafluoroethylene to give a solid product with the typical waxy appearance of polytetrafluoroethylene.

The Si–H bond in the compounds mentioned above is not hydrolysed on contact with water, but even 1% aqueous alkali is sufficient to cleave it with formation of hydrogen. The polyfluoroalkyl groups present are liberated rapidly and quantitatively as αω-di-H-polyfluoroalkanes, *e.g.*,

$$Me_2Si\begin{cases}C_2F_4H\\ [CF_2\cdot CF_2]_3\cdot H\end{cases} \xrightarrow{10\%\ aq.\ NaOH} CHF_2\cdot CHF_2 + H\cdot[CF_2\cdot CF_2]_3\cdot H$$

and the pseudo-halogen nature of the polyfluoroalkyl group in such compounds is again apparent.[1] This provides a convenient method for the analysis of mixture of isomers as illustrated in the Experimental part.

The reaction of a dialkylsilane with a fluoro-olefin thus provides a very convenient method for the formation of compounds containing one or more CF_2–Si bonds, with the polyfluoroalkyl group of a controlled chain length.

The boiling points of the tetrafluoroethyl silicon compounds are slightly higher than those of the corresponding unsubstituted compounds; *e.g.*, cf. Me_2SiHEt 43°, $Me_2SiH(CF_2\cdot CF_2H)$ 62°; Me_2SiEt_2 96°, $Me_2Si(CF_2\cdot CF_2H)_2$ 119°.

The Si–H stretching band in the infrared is characteristic and proved of particular value in the present work for ascertaining that the compounds of type (III) are free from compounds of type (II). The pseudo-halogen nature of the polyfluoroalkyl group when attached to silicon causes a shift of the Si–H absorption to shorter wavelength similar to that produced by chlorine as shown in the annexed Table.

Si–H *Stretching frequencies.*

$-CH_2-Si-H$		$Cl-Si-H$		$-CF_2-Si-H$	
Me_2SiH_2	2150	$MeSiHCl_2$	2220	$Me_2SiH\cdot[CF_2\cdot CF_2]\cdot H$	2190
$MeSiH_3$	2180, 2160	$SiHCl_3$	2250	$Me_2SiH[CF_2\cdot CF_2]_2\cdot H$	2190
SiH_4	2242, 2178, 2128			$Me_2SiH[CF_2\cdot CF_2]_3\cdot H$	2185

The $-CH_2$–Si–H, Cl–Si–H, and $-CF_2$–Si–H systems are thus characterised by Si–H absorption at 2150—2180, 2220—2250, and 2185—2200 respectively. Detailed discussion of the spectra of polyfluoroalkyl silicon compounds is deferred to a later paper.

Experimental

Photochemical reactions were carried out in sealed silica tubes or in the apparatus incorporating a 20 l. flask described and used earlier for the reaction of trifluoroiodomethane with nitric oxide.[4] There was no need to shake the 20 l. flask or to use mercury. Reaction times are undoubtedly excessive, and the greater part of the reaction is complete within 4—5 hr.

Dimethylsilane.—This was prepared in 67% yield from dimethyldichlorosilane (55 g., 0·425 mole) and excess of lithium aluminium hydride (10 g., 0·26 mole) in diethyl or di-*n*-butyl ether solution (100 ml.).[7] The product was condensed in traps cooled by liquid nitrogen and

[7] Finholt, Bond, Wilzbach, and Schlesinger, *J. Amer. Chem. Soc.*, 1947, **69**, 2692; Peake, Nebergall, and Yun-ti-chen, *ibid.*, 1952, **74**, 1526.

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freed from ether by distillation *in vacuo* (Found: *M*, 60. Calc. for C_2H_8Si: *M*, 60). Its purity was checked by infrared spectroscopy.

Dark Reaction of Dimethylsilane and Tetrafluoroethylene.—Dimethylsilane (4 mmoles) and tetrafluoroethylene (2 mmoles) failed to react when kept in a sealed 50 ml. Pyrex tube in the dark for 4 months.

Photochemical Reaction of Dimethylsilane with Tetrafluoroethylene.—(a) *In a silica tube under pressure.* Dimethylsilane (1·20 g., 20 mmoles) and tetrafluoroethylene (1·18 g., 11·80 mmoles) (mole-ratio $Me_2SiH_2 : C_2F_4 = 1·695 : 1$) were sealed in a 200 ml. silica tube and exposed to ultraviolet radiation from a Hanovia S 250 U type arc used without the filter. Rapid reaction ensued and liquid products were clearly detectable after 5 hr., but the irradiation was continued for a further 19 hr. Hydrogen was not detectable as a non-condensable gas by the sensitive vacuum techniques available, and all the tetrafluoroethylene had been used. The products were distilled *in vacuo* to give unchanged dimethylsilane (11·4 mmoles, 57%), dimethyl-(1 : 1 : 2 : 2-tetrafluoroethyl)silane (1·04 g., 6·35 mmoles, 54%), a mixture of the compounds $(CH_3)_2SiH·[CF_2·CF_2]_2·H$ and $(CH_3)_2Si(CF_2·CF_2H)_2$ (0·42 g., 1·61 mmoles, 27%), and a small residue. A small amount of an oil of higher b. p. remained in the reaction vessel. The polyfluoroalkyl silicon compounds were identified by comparison of their physical properties and infrared spectra with the analysed samples prepared as in (b) below. The analytical procedure used is described below.

In a second experiment, a large excess of dimethylsilane was used. Tetrafluoroethylene (1·40 g., 14 mmoles) and dimethylsilane (4·20 g., 70 mmoles) (mole-ratio $Me_2SiH_2 : C_2F_4 = 5 : 1$) were irradiated in a sealed 340 ml. silica tube for 24 hr. Distillation then gave unchanged dimethylsilane (80%) and liquid products (2·171 g.) which were fractionated to give (i) dimethyl-(1 : 1 : 2 : 2-tetrafluoroethyl)silane (1·852 g., 11·6 mmoles, 83%), b. p. 62—64°, and (ii) a residue (0·160 g., 9%) shown by analysis of the type outlined below to consist of dimethyl-(1 : 1 : 2 : 2 : 3 : 3 : 4 : 4-octafluorobutyl)silane (0·125 g., 78%) and dimethyldi-(1 : 1 : 2 : 2-tetrafluoroethyl)silane (0·035 g., 22%). The experiment has thus produced the compounds $Me_2SiH(C_2F_4H)$, $Me_2SiH·[C_2F_4]_2·H$, and $Me_2Si(C_2F_4H)_2$ in 83%, 7%, and 2% yield respectively.

(b) *In a 20 l. bulb at sub-atmospheric pressure.* Dimethylsilane (19·5 g., 0·325 mole) and tetrafluoroethylene (21·5 g., 0·215 mole) (mole-ratio $Me_2SiH_2 : C_2F_4 = 1·51 : 1$, total pressure 493 mm. at 20°) were transferred to the evacuated 20 l. bulb of the photochemical apparatus.[4] The ultraviolet lamp was inserted into the silica inner tube and as soon as it was switched on an immediate rapid reaction was apparent and a mist of fine globules of product formed in the bulb. After 4 hr. the liquid products had collected at the bottom of the bulb and reaction was essentially complete; irradiation was continued for a further 20 hr. without apparent change. Hydrogen was not detected as a reaction product. The more volatile products were pumped from the bulb and distilled to give (i) unchanged dimethylsilane (0·166 mole, 51%) (Found: *M*, 60), (ii) *dimethyl-(1 : 1 : 2 : 2-tetrafluoroethyl)silane* (16·13 g., 47%), b. p. 62·3° (Found: C, 29·7; H, 4·8%; *M*, 160. $C_4H_8F_4Si$ requires C, 30·0; H, 5·0%; *M*, 160), (iii) a mixture (7·52 g., 27%), b. p. 119° (Found: C, 27·4; H, 3·2. Calc. for $C_6H_6F_8Si$: C, 27·7; H, 3·1%), of dimethyldi-(1 : 1 : 2 : 2-tetrafluoroethyl)silane (1·88 g., 7·2 mmoles, 7%) and dimethyl-(1 : 1 : 2 : 2 : 3 : 3 : 4 : 4-octafluorobutyl)-silane (5·64 g., 21·6 mmoles, 20%), (iv) a mixture (2·17 g., 8%), b. p. 98°/70 mm. (Found: C, 26·4; H, 2·2. Calc. for $C_8H_8F_{12}Si$: C, 26·7; H, 2·2%), of dimethyl-(1 : 1 : 2 : 2 : 3 : 3 : 4 : 4-octafluorobutyl)-(1 : 1 : 2 : 2-tetrafluoroethyl)-silane (2·01 g., 5·60 mmoles, 8%) and (1 : 1 : 2 : 2 : 3 : 3 : 4 : 4 : 5 : 5 : 6 : 6-dodecafluorohexyl)dimethylsilane (0·16 g., 0·45 mmole, 0·5%), and (v) a viscous residue (18%) of higher b. p. (*i.e.*, more than $3C_2F_4$ units per dimethylsilane unit) obtained by draining the less-volatile products from the reaction flask and as a residue from the distillation.

Yields are based on tetrafluoroethylene, and the method of analysis of the mixtures is described below.

Reaction of Dimethyl-(1 : 1 : 2 : 2-tetrafluoroethyl)silane with Tetrafluoroethylene.—The polyfluoroalkylsilane (5·222 g., 32·6 mmoles) and tetrafluoroethylene (1·75 g., 17·5 mmoles) (mole-ratio 1·87 : 1), irradiated for 40 hr. in a sealed 200 ml. silica tube with the liquid phase shielded, gave unchanged dimethyl-(1 : 1 : 2 : 2-tetrafluoroethyl)silane (2·44 g., 15·3 mmoles, 47%), and *dimethyldi-(1 : 1 : 2 : 2-tetrafluoroethyl)silane* (4·05 g., 15·6 mmoles, 90% based on tetrafluoroethylene used), b. p. 120° (Found: C, 27·7; H, 2·9. $C_6H_8F_8Si$ requires C, 27·7; H, 3·1%). Infrared spectroscopic examination showed that Si–H bonds were absent. The small residue from the distillation (0·1 g.) was not examined.

Stability of Dimethyl-(1 : 1 : 2 : 2-tetrafluoroethyl)silane to Water.—The compound (0·234 g., 1·46 mmoles) was shaken in a 500-ml. bulb with water (10 ml.) for 1 hr. at 20°. Under such conditions the silicon compound is in the vapour phase. The bulb was connected to an apparatus for the manipulation of volatile compounds and opened; a non-condensable gas had not been produced. The volatile products were distilled to give only unchanged starting material (1·45 mmoles, 99%).

Alkaline Hydrolysis of Dimethyl-(1 : 1 : 2 : 2-tetrafluoroethyl)silane.—The compound (0·308 g., 1·925 mmoles) was shaken with 15% aqueous sodium hydroxide (10 ml.) at 20° for 10 min. The total volatile products were measured manometrically and the condensable fraction was then collected in a trap cooled by liquid oxygen. The non-condensable gas was hydrogen (1·90 mmoles, 99%) and the condensable gas was 1 : 1 : 2 : 2-tetrafluoroethane (1·90 mmoles, 99%) (Found: *M*, 102. Calc. for $C_2H_2F_4$: *M*, 102), identified spectroscopically.[1] A second experiment gave essentially the same results.

Alkaline Hydrolysis of Dimethyldi-(1 : 1 : 2 : 2-tetrafluoroethyl)silane.—The silane (0·1875 g., 0·72 mmole), shaken in a sealed tube with 10% aqueous sodium hydroxide (10 ml.) for 10 min., liberated 1 : 1 : 2 : 2-tetrafluoroethane (identified spectroscopically) essentially quantitatively, but no hydrogen.

Analytical Procedure for Mixtures of Products containing more than 1 C_2F_4 *Unit per Silicon Atom.*—(a) *A mixture containing* $Me_2SiH\cdot[C_2F_4]_2\cdot H$ *and* $Me_2Si(CF_2\cdot CHF_2)_2$. Preliminary qualitative experiments revealed that the mixture was decomposed by 1% aqueous sodium hydroxide at room temperature to give a mixture of hydrogen, $CHF_2\cdot CHF_2$, and $H\cdot[CF_2\cdot CF_2]_2\cdot H$. The last two compounds were identified by means of their vapour pressures, molecular weights, and infrared spectra.[1] In a typical analysis, the mixture (295·5 mg., 1·137 mmoles), shaken with 10% aqueous sodium hydroxide (10 ml.) at 20° for 10 min., gave hydrogen (0·845 mmole) as a non-condensable gas. The amount of the compound $Me_2SiH\cdot[C_2F_4]_2\cdot H$ present in the mixture (74%) is thus obtained directly, since only this compound can liberate hydrogen. The amount of $Me_2Si(CF_2\cdot CHF_2)_2$ is thus 26%. No attempt was made to separate the mixture of the compounds $H\cdot[CF_2\cdot CF_2]\cdot H$ and $H\cdot[CF_2\cdot CF_2]_2\cdot H$ obtained as a condensable gas (1·335 mmoles, 93%), but its average molecular weight was determined (Found: *M*, 153·6), and used to calculate the percentage of the gases present in the mixture and hence the composition of the original mixture: $Me_2SiH\cdot[C_2F_4]_2\cdot H$ 68%, $Me_2Si(CF_2\cdot CHF_2)_2$ 32%. The agreement between the two methods of analysis is considered adequate for this purpose, and the first analysis is probably more nearly correct. The accuracy could be improved considerably by use of more suitable gas-measuring equipment, and by heating the aqueous solution to help to expel the gases.

(b) *A mixture containing* $Me_2SiH\cdot[C_2F_4]_3\cdot H$ *and* $Me_2Si(CF_2\cdot CHF_2)(CF_2\cdot CF_2\cdot CF_2\cdot CHF_2)$, *with smaller amounts of* $Me_2SiH\cdot[C_2F_4]_2\cdot H$ *and* $Me_2Si(CF_2\cdot CHF_2)_2$. The mixture (959 mg.), shaken with 10% aqueous sodium hydroxide (20 ml.) at 20° for 10 min., gave hydrogen (0·65 mmole), $H\cdot[CF_2\cdot CF_2]\cdot H$ (2·32 mmoles), $H\cdot[CF_2\cdot CF_2]_2\cdot H$ (2·64 mmoles), and $H\cdot[CF_2\cdot CF_2]_3\cdot H$ (0·18 mmole). The condensable gases were fractionated *in vacuo* and the analysis of various fractions was carried out spectroscopically. The amount of $H\cdot[CF_2\cdot CF_2]_3\cdot H$ gives immediately the amount of $Me_2SiH\cdot[C_2F_4]_3\cdot H$ in the mixture (0·18 mmole, 65 mg.). The hydrogen produced arises from both $Me_2SiH\cdot[C_2F_4]_3\cdot H$ and $Me_2SiH\cdot[C_2F_4]_2\cdot H$, and since 0·18 mmole of the former is present, 0·47 mmole of the latter (122 mg.) must be present also. The $H\cdot[CF_2\cdot CF_2]_2\cdot H$ arises from both $Me_2SiH\cdot[C_2F_4]_2\cdot H$ and $Me_2Si(CF_2\cdot CHF_2)(CF_2\cdot CF_2\cdot CF_2\cdot CHF_2)$, and since 0·47 mmole of the former is present, there must be 2·17 mmoles of the latter (780 mg.). The $H\cdot[CF_2\cdot CF_2]\cdot H$ arises from both $Me_2Si(CF_2\cdot CHF_2)(CF_2\cdot CF_2\cdot CF_2\cdot CHF_2)$ and $Me_2Si(CF_2\cdot CHF_2)_2$, and since 2·17 mmoles of the former are present, there must be 0·15 mmole of $H\cdot[CF_2\cdot CF_2]\cdot H$ arising from 0·075 mmole of the latter (18 mg.), each molecule of which yields two of $H\cdot[CF_2\cdot CF_2]\cdot H$ on hydrolysis. The analytical figures lead to an apparent total weight for the original mixture of 985 mg.; *i.e.*, the error is approx. 3%.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, September 17th,* 1956].

XUM

204. *Polonium Monosulphide.*

By K. W. Bagnall and D. S. Robertson.

Polonium monosulphide has been prepared on the milligram scale; its decomposition under vacuum has been used as the basis of a new method for the preparation of pure polonium metal.

Tracer studies [1] have shown that polonium can be precipitated from acid solution together with other insoluble sulphides by hydrogen sulphide. The composition of the precipitate was, however, uncertain although Guillot [2] had suggested that it was polonium sesquisulphide, presumably analogous to bismuth sulphide; analytical data could not be produced to support this assumption owing to the very small amounts of polonium then available. More recently, the precipitation of milligram amounts of polonium from dilute hydrochloric acid solution was found to yield a black solid, which was not analysed owing to the presence of large amounts of sulphur resulting from the radiation-induced oxidation of the hydrogen sulphide. Since the black solid yielded a sublimate of polonium metal when heated in a vacuum it was possible that the precipitate was elementary polonium.[3] The attempted preparation of a sulphide from the elements has also been reported, but this was unsuccessful.[4]

The decomposition of the sulphide precipitate into the elements has been investigated in some detail since it affords a convenient and rapid method of preparing pure, lead-free polonium in good yield from aged polonium residues, the precipitated lead sulphide being involatile under the conditions used for the sublimation of the polonium. The procedure is, however, useless for the separation of polonium from irradiated bismuth since bismuth sulphide decomposes appreciably to the metal at 500° and 5 μ pressure, the resulting sublimate consisting of a mixture of bismuth and its sulphide. The separation of tracer polonium from bismuth–polonium sulphide precipitates at 700° under vacuum [1] cannot, therefore, have been very efficient.

The analytical data obtained in the present work show that the black precipitate obtained by passing hydrogen sulphide into a solution of polonium dichloride or tetrachloride in dilute hydrochloric acid is the monosulphide, PoS. The first step in the precipitation from solutions of the tetrachloride is evidently reduction to the bivalent state and this appears to be confirmed by experiments on the precipitation from solutions in concentrated (*ca.* 6N) hydrochloric acid, when it was found that very little polonium was precipitated, owing to the repression of the ionisation of the hydrogen sulphide, and the solution became pink, a characteristic of solutions of bivalent polonium.

The monosulphide is soluble in concentrated hydrochloric acid, insoluble in ethyl alcohol, acetone, or toluene and is decomposed by bromine, sodium hypochlorite, and aqua regia. It is also insoluble in ammonium sulphide, as previously reported for tracer polonium.[1]

The solubility product of polonium monosulphide was determined by precipitating the compound from solutions of varying hydrochloric acid concentration which had been saturated with hydrogen sulphide; the polonium concentration was determined by α-particle counting and the sulphide ion concentration was calculated from the solubility data of Kendall and Andrews [5] and the known dissociation constants of hydrogen sulphide. Activity corrections were not applied. The results are given in the Table, but the reproducibility was not good and the attainment of equilibrium required some time, during which a considerable amount of sulphur was precipitated owing to the oxidation

[1] Curie and Curie, *Compt. rend.*, 1898, **127**, 175.
[2] Guillot, *J. Chim. phys.*, 1931, **28**, 107.
[3] Bagnall, D'Eye, and Freeman, *J.*, 1955, 2320.
[4] Burbage, *Record Chem. Progr.*, 1953, **44**, 157.
[5] Kendall and Andrews, *J. Amer. Chem. Soc.*, 1921, **43**, 1545.

of the hydrogen sulphide by radiation; this could lead to anomalous solubility results if any of the polonium was carried down with the sulphur. All the determinations were made with freshly prepared, lead-free polonium.

Concn. of HCl	Concn. of polonium mc/ml.	Concn. of polonium moles/l. $\times 10^6$	Concn. of sulphide ion (moles/l.) (calc.)	Solubility product
N	4·7	5·03	$1·09 \times 10^{-23}$	$5·5 \times 10^{-29}$
2N	18·5	19·8	$2·73 \times 10^{-24}$	$5·4 \times 10^{-29}$
4·4N	90·0	96·4	$2·65 \times 10^{-25}$	$5·5 \times 10^{-29}$

The monosulphide decomposes into the elements at about 275° and 5 μ pressure at which temperature the sulphur sublimes from the residue of lead sulphide and polonium metal. The latter can be sublimed from the lead sulphide at 450—500° at the same pressure giving an extremely pure product. *X*-Ray powder photographs of the metal so prepared were much better than those of the metal obtained as reported earlier [6] and the specimens of metal could be easily melted under vacuum to form small silvery globules. The *X*-ray powder photographs of the monosulphide were unfortunately too poor to index.

The formation of polonium monosulphide is in marked contrast to the rather ill-defined behaviour of the tellurium–sulphur system and is further evidence of the increased basic character of polonium expected from its position in the Periodic Table.

Experimental

All the work was carried out in dry-boxes in order to minimise the hazards associated with the handling of high levels of α-activity.

Analytical.—Specimens for analysis were precipitated from dilute (1—2N) hydrochloric acid solution, filtered through a 1 cm. diameter sintered disc (No. 3 or No. 4 porosity) and washed with a mixture of equal volumes of toluene and absolute alcohol (3 × 1 ml.) to remove precipitated sulphur. Some of the preparations were then dissolved in a 3 : 1 (v/v) nitric acid–hydrochloric acid oxidising mixture (0·2 ml.) containing a little bromine; the resulting solution was boiled for 15 min. with 1 ml. of concentrated hydrochloric acid in order to eliminate the bromine and the nitric acid. The solution was then analysed for sulphate and polonium by the methods used for the polonium sulphates.[7] Other specimens were analysed by heating the sulphide under vacuum and collecting the sulphur and polonium sublimates. The separation was quite efficient, the sulphur sublimate containing a maximum of 0·2% of the polonium. The sulphur was then estimated by oxidation to sulphate and analysis as above; preliminary experiments on the oxidation of milligram amounts of sulphur had shown that this procedure was quantitative. The polonium was determined by calorimetry and also by dissolving the metal in hydrochloric acid and counting α-particles from aliquot portions of the solution. The results obtained by the second procedure for the determination of sulphur were low [S : Po (g.-atom) = 0·85—0·90] for samples containing between 250 and 500 μg. of polonium monosulphide; this is probably due to the comparatively high vapour pressure of sulphur at room temperature. The S : Po ratios for the larger specimens were 1·00 ± 0·04, and the specimens analysed ranged in weight from 125 μg. to 3·6 mg. (approx. 15 curies of ^{210}Po).

Solubility Determinations.—The techniques used for the polonium sulphates [7] were used.

Application as a Purification Procedure.—The polonium is best precipitated from N-hydrochloric acid solution containing at least 100 mc/ml. of ^{210}Po; more dilute solutions should be concentrated by precipitation with lanthanum hydroxide before treatment with hydrogen sulphide. The attempted precipitation of the polonium from dilute solution (20 mc/ml.) with lead carrier gave poor yields. The precipitated sulphide is " unwettable " and tends to float on the surface of the liquid and stick to the walls of the glass tube in which the precipitation is carried out; this is overcome by adding a little alsolute alcohol or alcohol–toluene. The sulphide precipitate was filtered off on a No. 3 porosity filter stick mounted on a modified Buchner flask, washed with alcohol–toluene to remove sulphur, and then sealed into a distillation tube of the type described earlier.[3]

The sulphide was decomposed by heating at 275° for 10 min., and the polonium distilled by heating at 450—500° for 15 min.; the metal was then sealed off under vacuum until required.

[6] Bagnall and D'Eye, *J.*, 1954, 4295.
[7] Bagnall and Freeman, *J.*, 1956, 4579.

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The filter sticks can be re-used a number of times. The micro-filter sticks described in an earlier paper [3] can be used for smaller (1 c) preparations. The time required for the complete purification cycle is less than 1 hr. and the overall recoveries at the curie level are in the range 96—99% and depend on the precipitation efficiency, since the distillation efficiency is about 99·7%. The method compares favourably with other procedures used for the purification of polonium and it provides a very pure product.

ATOMIC ENERGY RESEARCH ESTABLISHMENT,
HARWELL, BERKS.

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205. *Some Steroidal* 1 : 4-*Diene*-3 : 11-*diones and* 1 : 4 : 6-*Triene*-3 : 11-*diones.**

By D. N. KIRK, D. K. PATEL, and V. PETROW.

Hecogenin acetate (IV; R = R′ = H) has been converted into 5α : 25*D*-spirostan-3 : 11-dione (III; R = R′ = H) and thence by the appropriate bromination–dehydrobromination sequences into the corresponding 1-ene (I; R = H, R′ = Br), 4-ene (IX; R = H), 1 : 4-diene (VII; R = H), and 1 : 4 : 6-triene (XI; R = Br).

3β-Acetoxy-5α-pregnane-12 : 20-dione, obtained from hecogenin, has been similarly converted into pregna-1 : 4 : 16-triene-3 : 11 : 20-trione (XVIII).

Attempts to enforce the dienone– or trienone–phenol rearrangement on the above ketones by toluene-*p*-sulphonic acid in acetic anhydride proved unsuccessful.

WE were interested in extending the dienone– and trienone–phenol rearrangement to 11-oxo-steroids. To this end we have prepared 25D-spirosta-1 : 4-diene-3 : 11-dione (VII; R′ = H), 23ξ-bromo-25*D*-spirosta-1 : 4 : 6-triene-3 : 11-dione (XI; R′ = Br), and pregna-1 : 4 : 16-triene-3 : 11 : 20-trione (XVIII) from hecogenin.

11α : 23ξ-Dibromohecogenin acetate (IV; R = R′ = Br) [1] was converted into 23ξ-bromo-11β- : 12β-epoxy-5α : 25*D*-spirostan-3β-ol (V) [2,3] by reduction with sodium borohydride and alkaline hydrolysis. Reaction of the epoxide (V) with hydrobromic acid gave the bromohydrin, which was not isolated but was converted directly into 12α : 23ξ-dibromo-5α : 25*D*-spirostan-3 : 11-dione (III; R = R′ = Br) by oxidation with chromic acid. The constitution assigned to the dione (III; R = R′ = Br) was confirmed by its debromination with zinc dust to 5α : 25*D*-spirostan-3 : 11-dione [4] (III; R = R′ = H). Partial debromination with zinc dust in cold benzene–acetic acid gave the 23ξ-monobromo-derivative (III; R = H, R′ = Br) in good yield.

Bromination of the 3 : 11-diones (III; R = R′ = H; R = R′ = Br; and R = H, R′ = Br) was next examined.

5α : 25*D*-Spirostan-3 : 11-dione (III; R = R′ = H) reacted rapidly with one molar equivalent of bromine in acetic acid, to give an inseparable mixture of products. With two molar equivalents, in contrast, a single dibromo-derivative was obtained, which differed from the 12α : 23ξ-dibromo-dione (III; R = R′ = Br). The same dibromo-derivative was also obtained by monobromination of 23ξ-bromo-5α : 25*D*-spirostan-3 : 11-dione (III; R = H, R′ = Br), thereby revealing the presence in it of a 23ξ-bromo-substituent. Its constitution as 2α : 23ξ-dibromo-5α : 25*D*-spirostan-3 : 11-dione (VIII; R = H) followed from its dehydrobromination by boiling collidine to 23ξ-bromo-5α : 25*D*-spirost-1-en-3 : 11-dione (I; R = H, R′ = Br) ($\lambda_{max.}$ 227 mμ), and its conversion by

* Cf. Callow and James (*J.*, 1956, 4744) who have independently reported the conversion of 3β-acetoxy-5α-pregn-16-ene-12 : 20-dione into 5α-pregnane-3 : 11 : 20-trione by an identical route.

[1] Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 303; Mueller, Stobaugh and Winniford, *J. Amer. Chem. Soc.*, 1951, **73**, 2400.
[2] Cornforth, Osbond, and Phillipps, *J.*, 1954, 907.
[3] Schmidlin and Wettstein, *Helv. Chim. Acta*, 1953, **36**, 1241.
[4] Djerassi, Ringold, and Rosenkranz, *J. Amer. Chem. Soc.*, 1951, **73**, 5513.

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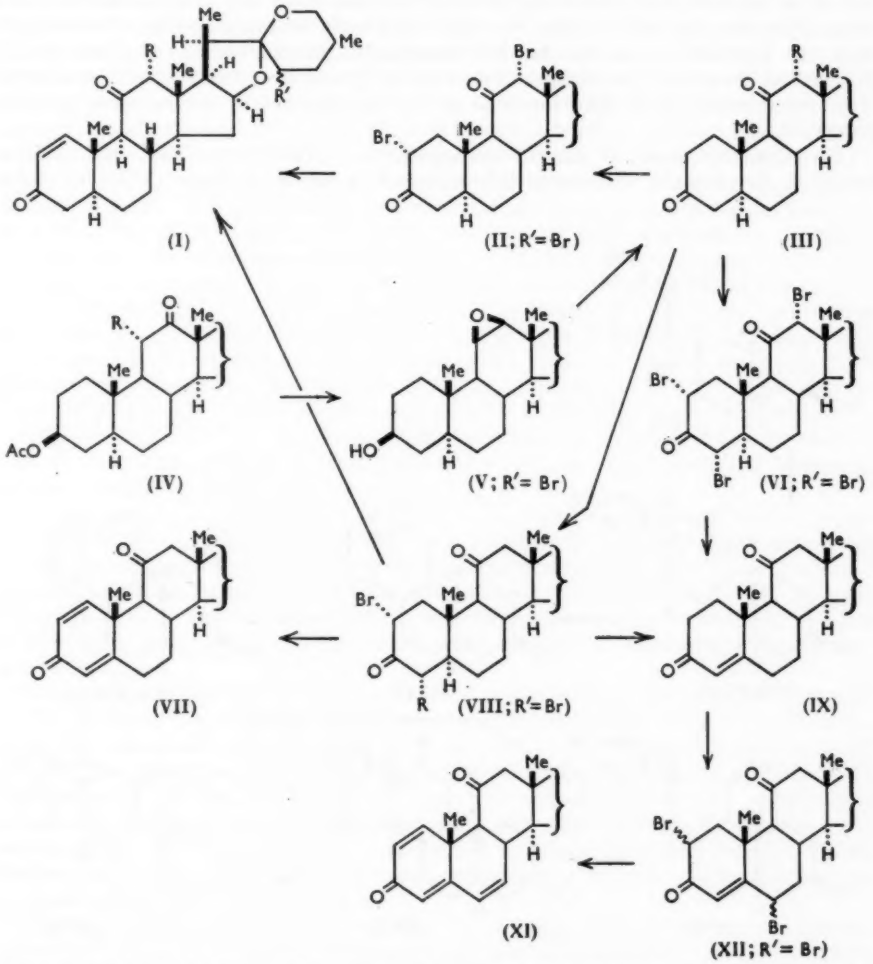
2 : 4-dinitrophenylhydrazine in acetic acid [5] into 23ξ-bromo-5α : 25*D*-spirost-1-en-3 : 11-dione 2 : 4-dinitrophenylhydrazone ($\lambda_{max.}$ 375 mμ). The α-configuration of the 2-halogen atom is rendered likely by precedent.[6]

Reaction of 12α : 23ξ-dibromo-5α : 25*D*-spirostan-3 : 11-dione (III; R = R′ = Br) with one molar equivalent of bromine in acetic acid led to the formation of 2α : 12α : 23ξ-tribromo-5α : 25*D*-spirostan-3 : 11-dione (II). The constitution assigned to this compound followed from (i) its conversion into 12α : 23ξ-dibromo-5α : 25*D*-spirost-1-en-3 : 11-dione (I; R = R′ = Br) ($\lambda_{max.}$ 225 mμ) by treatment with semicarbazide and



cleavage of the derived semicarbazone with *p*-hydroxybenzaldehyde,[7] and (ii) its conversion into the 2 : 4-dinitrophenylhydrazone of the ketone (I; R = R′ = Br) ($\lambda_{max.}$ 373—375 mμ) by reaction with 2 : 4-dinitrophenylhydrazine. Partial debromination of the dibromide

[5] Djerassi, *J. Amer. Chem. Soc.*, 1949, **71**, 1003.
[6] Jones, Ramsay, Herling, and Dobriner, *ibid.*, 1952, **74**, 2828.
[7] McGuckin and Kendall, *ibid.*, 1952, **74**, 5811; Kritchevsky, Carmaise, and Gallagher, *ibid.*, p. 483.

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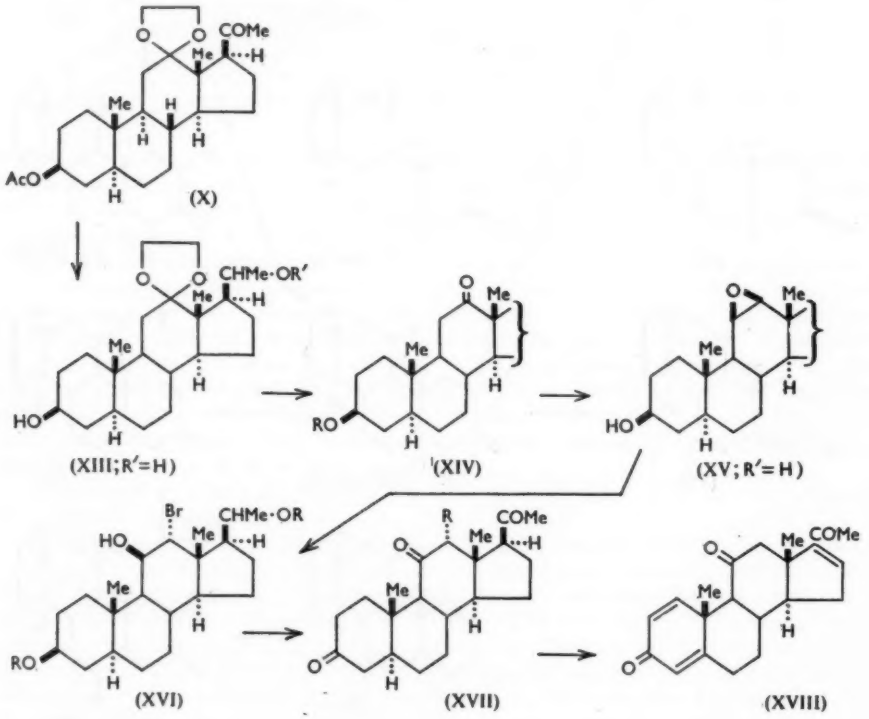
(I; R = R′ = Br) with zinc dust in cold benzene–acetic acid gave 23ξ-bromo-5α : 25*D*-spirost-1-en-3 : 11-dione (I; R = H, R′ = Br), also prepared (above) by dehydrobromination of the 2α : 23ξ-dibromo-compound (VIII; R = H) with boiling collidine.

Bromination of 23ξ-bromo-5α : 25*D*-spirostan-3 : 11-dione (III; R = H, R′ = Br) with two molar equivalents of bromine, followed immediately by isolation of the products, failed to yield a homogeneous bromo-derivative. After 16—20 hours, however, a green or purple solution was obtained which readily gave a tribromide in good yield. The same compound was subsequently obtained by treating 5α : 25*D*-spirostan-3 : 11-dione (III; R = R′ = H) with three molar equivalents of bromine under similar experimental conditions. The slow appearance of the new tribromide in the bromination liquors is consistent with its formulation as 2α : 4α : 23ξ-tribromo-5α : 25*D*-spirostan-3 : 11-dione (VIII; R = Br) (cf. Jones *et al.*[6] for configuration of the halogen atoms), produced by isomerisation of an intermediate 2 : 2 : 23ξ-tribromide under the influence of the hydrogen bromide present.[8]

Dehydrobromination of the tribromo-derivative (VIII; R = Br) with collidine furnished the required 23ξ-bromo-25*D*-spirosta-1 : 4-dien-3 : 11-dione (VII; R′ = Br),



$\lambda_{max.}$ 239 mμ (in EtOH), characterised by the formation of a 2 : 4-dinitrophenylhydrazone, $\lambda_{max.}$ 389 mμ (in EtOH). Reaction of the tribromo-derivative (VIII; R = Br) with sodium iodide in boiling acetone for 24 hours, followed by gentle de-iodination of the product with zinc dust,[9] furnished 23ξ-bromo-25*D*-spirost-4-en-3 : 11-dione (IX; R′ = Br),

[8] Djerassi and Scholz, *J. Amer. Chem. Soc.*, 1947, **69**, 2404.
[9] Rosenkranz, Mancera, Gatica, and Djerassi, *ibid.*, 1950, **72**, 4077.

$\lambda_{max.}$ 238 mμ (in EtOH), in low yield. The last compound was additionally obtained by dibromination of the 12α : 23ξ-dibromo-derivative (III; R = R′ = Br) under the foregoing experimental conditions, to yield 2α : 4α : 12α : 23ξ-tetrabromo-5α : 25*D*-spirostan-3 : 11-dione (VI), followed by reaction with sodium iodide in acetone and subsequent dehalogenation. *Inter alia*, we examined the action of collidine on the tetrabromo-derivative (VI), but found that, in common with other 12-bromo-11-ones we had previously examined, it gave only an acid-soluble tar.

Dibromination of the ketone (IX; R′ = Br) gave 2 : 6 : 23ξ-tribromo-25*D*-spirost-4-en-3 : 11-dione (XII) (cf. Djerassi *et al.*).[10] Attempts to convert this compound into 23ξ-bromo-25*D*-spirosta-1 : 4 : 6-triene-3 : 11-dione (XI; R′ = Br) by hot collidine gave a product consisting essentially of the required trienedione but contaminated with a more highly brominated impurity as shown by its analysis and ultraviolet absorption spectrum.

Surprisingly, attempted debromination of 23ξ-bromo-25*D*-spirosta-1 : 4-diene-3 : 11-dione (VII; R′ = Br) with zinc in acetic acid gave a non-ketonic product which failed to yield a crystalline fraction after chromatography. Similar reduction of cholesta-1 : 4-dien-3-one gave a gum which furnished *ca.* 10% of a new hydrocarbon, $C_{27}H_{42-44}$, on chromatography. This hydrocarbon showed ultraviolet absorption maxima (in propan-2-ol) at 250, 336, and 352 mμ, but gave evidence of only one ethylenic linkage on perbenzoic acid titration. Its structure remains obscure. No better results were obtained by using zinc dust or a zinc–copper couple in ethanol, whilst catalytic methods led to saturation of the ethylenic linkages. Reductive removal of the 23ξ-bromine atom without concomitant destruction of the 1 : 4-dien-3-one system was ultimately achieved by using sodium iodide in hot acetic acid. In this way the dienone (VII; R′ = Br) was converted into 25*D*-spirosta-1 : 4-diene-3 : 11-dione (VII; R′ = H), $\lambda_{max.}$ 238 mμ (in EtOH). Debromination of the 23ξ-bromo-1 : 4 : 6-triene-3 : 11-dione (XI; R′ = Br) could not be achieved.

The 4-en-3-one (IX; R′ = Br) was similarly reduced to 25*D*-spirost-4-en-3 : 11-dione (IX; R′ = H), $\lambda_{max.}$ 237 mμ (in EtOH), although in this case removal of the halogen atom was also accomplished with zinc–acetic acid.

5α-Pregnane-3 : 11 : 20-trione [11] (XVII; R = H), required for conversion into pregna-1 : 4 : 16-triene-3 : 11 : 20-trione (XVIII), was prepared by converting hecogenin into 11-oxotigogenin and degrading the latter to 3β-acetoxy-5α-pregn-16-ene-11 : 20-dione.[12] Catalytic reduction, hydrolysis and oxidation gave the required trione (XVII; R = H). The overall yield, however, was disappointing. More encouraging results were obtained by effecting removal of the spiroketal side-chain before transference of the 12-oxo-group to the 11-position.

Hecogenin acetate (IV; R = R′ = H) was converted into 3β-acetoxy-5α-pregn-16-ene-12 : 20-dione,[13] and thence into 3β-acetoxy-5α-pregnane-12 : 20-dione.[14] Reaction of the last compound with ethylene glycol and the boron trifluoride–ether complex [15] gave the 12 : 12-ethylenedioxy-derivative (X), which passed into 12 : 12-ethylenedioxy-5α-pregnane-3β : 20ξ-diol (XIII) on reduction with sodium borohydride. Removal of the 12 : 12-ethylenedioxy-group with aqueous acetic acid gave 3β : 20ξ-dihydroxy-5α-pregnan-12-one (XIV; R = R′ = H), converted by acetic anhydride–pyridine in the cold into the 3-monoacetate (XIV; R = Ac; R′ = H) and on prolonged heating into the 3 : 20-diacetate (XIV; R = R′ = Ac).

The monoacetate (XIV; R = Ac, R′ = H) was smoothly converted by 1 molar equivalent of bromine into the 11α-bromo-derivative, admixed with a smaller quantity of the readily removed 11β-bromo-isomer (cf. ref. 2). The diacetate (XIV; R = R′ = Ac),

[10] Djerassi, Rosenkranz, Romo, Kaufmann, and Pataki, *J. Amer. Chem. Soc.*, p. 4534.
[11] Stork, Romo, Rosenkranz, and Djerassi, *ibid.*, 1951, **73**, 3546.
[12] Djerassi, Batres, Romo, and Rosenkranz, *ibid.*, 1952, **74**, 3634.
[13] Wagner, Moore, and Forker, *ibid.*, 1950, **72**, 1856; Cameron, Evans, Hamlet, Hunt, Jones, and Long, *J.*, 1955, 2807.
[14] Adams, Kirk, Patel, Petrow, and Stuart-Webb, *J.*, 1954, 2209.
[15] *Idem*, *ibid.*, p. 2298.

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in contrast, gave a lower yield of the 11α-bromo-isomer. Reduction of 3β-acetoxy-11α-bromo-20ξ-hydroxy-5α-pregnan-12-one with sodium borohydride, followed by alkaline hydrolysis, gave 11β : 12β-epoxy-5α-pregnane-3β : 20ξ-diol (XV), smoothly converted by hydrogen bromide into 12α-bromo-5α-pregnane-3β : 11β : 20ξ-triol (XVI; R = H). Chromic acid oxidation of the last compound furnished 12α-bromo-5α-pregnane-3 : 11 : 20-trione (XVII; R = Br), which gave 5α-pregnane-3 : 11 : 20-trione (XVII; R = H) in nearly quantitative yield on reduction with zinc dust in benzene–acetic acid. Tribromination of this product, followed by dehydrobromination of the crude tribromo-derivative with collidine (cf. Rubin *et al.*) [16] gave the required pregna-1 : 4 : 16-triene-3 : 11 : 20-trione, $\lambda_{max.}$ 236 mμ (in Pr^{i}OH), characterised as the bisdinitrophenylhydrazone, $\lambda_{max.}$ 385—386 mμ (in Pr^{i}OH).

The foregoing dienic ketones failed to undergo the dienone–heterophenol rearrangement [17] under the usual conditions of heating with toluene-*p*-sulphonic acid and acetic anhydride. No better result was obtained with the trienic ketone, there being no evidence of the normal trienone–phenol rearrangement.[18]

This observation argues for a lower reactivity of the 1 : 4-dien-3-one system owing, presumably, to the (−*I*) inductive effect of the 11-oxo-group. This view is supported by comparison of the ultraviolet absorption maxima of the above dienones and trienones with their 11-deoxy-analogues: a significant hypsochromic shift associated with the presence of the 11-oxo-group in the molecule is clearly to be seen.

Experimental

Optical rotations were measured on $CHCl_3$ solutions in a 1 dm. tube unless otherwise stated. Ultraviolet absorption spectra were kindly determined by Mr. M. Davies, B.Sc.

12α : 23ξ-*Dibromo*-5α : 25D-*spirostan*-3 : 11-*dione* (III; R = R′ = Br).—11α : 23ξ-Dibromohecogenin acetate (IV; R = R′ = Br) [1] was converted into 23ξ-bromo-11β : 12β-epoxy-5α : 25*D*-spirostan-3β-ol (V) essentially by the method of Cornforth *et al.*[2] The bromo-compound (45 g.) in dioxan (450 ml.) was treated with 48% aqueous hydrobromic acid (67·5 ml.) in dioxan (135 ml.) and water (5 ml.). After 16 hr. at room temperature the mixture was poured into water (2 l.), and the product isolated with methylene chloride (3 × 300 ml.), to which was then added with vigorous stirring a solution of chromium trioxide (45 g.) in water (135 ml.) and acetic acid (270 ml.). Stirring was continued for 7 hr. after which the mixture was poured into water and the product isolated from the non-aqueous layer. Purification from ethanol gave 12α : 23ξ-*dibromo*-5α : 25*D*-*spirostan*-3 : 11-*dione*, needles, m. p. 209°, $[\alpha]_D^{27}$ −69° (*c* 0·52) (Found: C, 55·4; H, 6·7; Br, 27·2. $C_{27}H_{38}O_4Br_2$ requires C, 55·3; H, 6·5; Br, 27·3%).

23ξ-*Bromo*-5α : 25D-*spirostan*-3 : 11-*dione* (III; R = H, R′ = Br).—The foregoing compound (25 g.) in benzene (500 ml.) and acetic acid (250 ml.) was stirred and treated with zinc dust (50 g.) added in four portions at intervals of 15 min. at <30°. After a further 15 min. the mixture was filtered, the solids were washed with acetic acid (50 ml.), and the filtrate and washings poured into water. The benzene layer yielded 23ξ-*bromo*-5α : 25D-*spirostan*-3 : 11-*dione*, plates, m. p. 232—234°, $[\alpha]_D^{24}$ −19° (*c* 0·41) (Found: C, 63·5; H, 7·7; Br, 15·3. $C_{27}H_{39}O_4Br$ requires C, 63·8; H, 7·7; Br, 15·7%), after crystallisation from chloroform–ethanol.

5α : 25D-*Spirostan*-3 : 11-*dione* (III; R = R′ = H).—12α : 23ξ-Dibromo-5α : 25*D*-spirostan-3 : 11-dione (5 g.) in acetic acid (50 ml.) and sodium acetate (10 g.) was heated under reflux with zinc dust (20 g.) for 1·5 hr. The product, isolated as above, crystallised from aqueous ethanol, to give 5α : 25*D*-spirostan-3 : 11-dione, needles, m. p. 237—239°, $[\alpha]_D^{24}$ −19° (*c* 0·57) (Found: C, 75·6; H, 9·4. Calc. for $C_{27}H_{40}O_4$: C, 75·7; H, 9·4%).

2α : 23ξ-*Dibromo*-5α : 25D-*spirostan*-3 : 11-*dione* (VIII; R = H).—(*a*) 5α : 25*D*-Spirostan-3 : 11-dione (4 g.) in acetic acid (200 ml.) was treated dropwise with bromine in acetic acid (17·5 ml. of 1·08M). 2α : 23ξ-*Dibromo*-5α : 25D-*spirostan*-3 : 11-*dione* was isolated with methylene chloride as needles, m. p. 214—216°, $[\alpha]_D^{25}$ −22° (*c* 0·448) (Found: C, 55·9; H, 6·8; Br, 28·6.

[16] Rubin, Wishinsky, and Bompard, *J. Amer. Chem. Soc.*, 1951, **73**, 2338.
[17] Woodward and Singh, *ibid.*, 1950, **72**, 494; Dreiding and Voltman, *ibid.*, 1954, **76**, 537.
[18] Djerassi and Rosenkranz, *J. Org. Chem.*, 1950, **15**, 896; Djerassi, Rosenkranz, Romo, Pataki, and Kaufmann, *J. Amer. Chem. Soc.*, 1950, **72**, 4540.

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$C_{27}H_{36}O_4Br_2$ requires C, 55·3; H, 6·5; Br, 29·3%), after crystallisation from methylene chloride–methanol. (*b*) 23ξ-Bromo-5α : 25*D*-spirostan-3 : 11-dione (1 g.) in acetic acid (50 ml.) was treated with bromine in acetic acid (8·3 ml. of 0·24M), to give the dibromo-derivative, m. p. 214—216°, alone or on admixture with a sample prepared as under (*a*).

23ξ-*Bromo*-5α : 25D-*spirost*-1-*en*-3 : 11-*dione* (I; R = H, R′ = Br).—(*a*) 2α : 23ξ-Dibromo-5α : 25D-spirostan-3 : 11-dione (2 g.) in collidine (16 ml.) was heated under reflux in nitrogen for 1 hr. The product was isolated with benzene, and the benzene solution was percolated through chromatographic alumina (10 g.; B.D.H.). Purification of the product from methylene chloride–methanol gave 23ξ-*bromo*-5α : 25D-*spirost*-1-*en*-3 : 11-*dione*, plates, m. p. 226—227°, $[\alpha]_D^{25}$ +7° (*c* 0·640), $\lambda_{max.}$ 227 mμ (log ε 4·00 in EtOH) (Found: C, 64·4; H, 7·4; Br, 15·4. $C_{27}H_{37}O_4Br$ requires C, 64·2; H, 7·4; Br, 15·8%).

(*b*) 12α : 23ξ-Dibromo-5α : 25*D*-spirost-1-en-3 : 11-dione (150 mg.) (see below) in acetic acid (3 ml.) and benzene (5 ml.) was shaken with zinc dust (1 g.) at room temperature for ½ hr. The product, after purification from methylene chloride–methanol, was identified with the preceding compound.

(*c*) 2α : 23ξ-Dibromo-5α : 25*D*-spirostan-3 : 11-dione (250 mg.) in acetic acid (10 ml.) and chloroform (3 ml.) was heated with 2 : 4-dinitrophenylhydrazine (150 mg.) and sodium acetate (60 mg.) at 60° under nitrogen for ½ hr. After removal of the chloroform, the mixture was allowed to cool, 23ξ-*bromo*-5α : 25D-*spirost*-1-*en*-3 : 11-*dione* 3-(2 : 4-*dinitrophenylhydrazone*) separating in orange-red leaflets, m. p. 255—258°, $\lambda_{max.}$ 375 mμ (log ε 4·49 in $CHCl_3$) (Found: N, 8·4; Br, 10·9. $C_{33}H_{41}O_7N_4Br$ requires N, 8·2; Br, 11·6%), after crystallisation from chloroform–ethyl acetate.

2α : 12α : 23ξ-*Tribromo*-5α : 25D-*spirostan*-3 : 11-*dione* (II), needles, m. p. 204—208°, $[\alpha]_D^{23}$ −71° (*c* 0·602) (Found: C, 48·8; H, 5·7; Br, 35·8. $C_{27}H_{37}O_4Br_3$ requires C, 48·7; H, 5·6; Br, 36·0%), after crystallisation from methylene chloride–methanol, was prepared by treating 12α : 23ξ-dibromo-5α : 25*D*-spirostan-3 : 11-dione (2 g.) in acetic acid (50 ml.) with bromine in acetic acid (16 ml. of 0·214M) and isolating the product with methylene chloride.

12α : 23ξ-*Dibromo*-5α : 25D-*spirost*-1-*en*-3 : 11-*dione* (I; R = R′ = Br).—The foregoing compound (250 mg.), semicarbazide hydrochloride (50 mg.), and sodium acetate (40 mg.) in 90% acetic acid (10 ml.) were heated on the steam-bath under nitrogen for 1 hr. A solution of *p*-hydroxybenzaldehyde (2·5 g.) and sodium acetate (40 mg.) in 50% acetic acid (20 ml.) was then added and heating continued for 2 hr. The product, isolated with ether, was purified from methylene chloride–methanol, to give 12α : 23ξ-*dibromo*-5α : 25D-*spirost*-1-*en*-3 : 11-*dione*, plates, m. p. 225°, $[\alpha]_D^{24}$ −57° (*c* 0·856), $\lambda_{max.}$ 225 mμ (log ε 4·06 in EtOH) (Found: Br, 28·3. $C_{27}H_{36}O_4Br_2$ requires Br, 27·4%).

The 3-(2 : 4-*dinitrophenylhydrazone*), m. p. 245—247°, $\lambda_{max.}$ 373—375 mμ (log ε 4·46 in PrⁱOH) (Found: Br, 20·2; N, 6·8. $C_{33}H_{40}O_7N_4Br_2$ requires Br, 20·9; N, 7·3%), from ethyl acetate–chloroform, was obtained by heating the tribromo-derivative (II) (250 mg.), 2 : 4-dinitrophenylhydrazine (150 mg.), anhydrous sodium acetate (60 mg.), acetic acid (7 ml.), and chloroform (4 ml.) at 60° under nitrogen for ½ hr.

2α : 4α : 23ξ-*Tribromo*-5α : 25D-*spirostan*-3 : 11-*dione* (VIII; R = Br).—23ξ-Bromo-5α : 25*D*-spirostan-3 : 11-dione (15 g.) in acetic acid (1 l.) was treated with bromine in acetic acid (57·5 ml. of 1·05M) during ½ hr., after which a 50% (w/v) solution (10 ml.) of hydrogen bromide in acetic acid was added. After being kept overnight at room temperature the blue solution was poured into water, and the product isolated with methylene chloride. Trituration with ether, followed by crystallisation from methylene chloride–methanol gave 2α : 4α : 23ξ-*tribromo*-5α : 25D-*spirostan*-3 : 11-*dione*, plates, m. p. 202—205°, $[\alpha]_D^{22}$ −21° (*c* 0·592) (Found: C, 49·1; H, 5·6; Br, 35·1. $C_{27}H_{37}O_4Br_3$ requires C, 48·7; H, 5·6; Br, 36·0%). The same compound was also obtained by treating 5α : 25*D*-spirostan-3 : 11-dione (4·0 g.) in acetic acid (200 ml.) with bromine in acetic acid (26·8 ml. of 1·05M) overnight at room temperature.

23ξ-*Bromo*-25D-*spirosta*-1 : 4-*diene*-3 : 11-*dione* (VII; R′ = Br).—The foregoing compound (8·5 g.) in collidine (60 ml.) was heated under reflux under nitrogen for 1·5 hr. The product in benzene solution was percolated through chromatographic alumina (30 g.; B.D.H.) and subsequently purified from methylene chloride–methanol, to give 23ξ-*bromo*-25D-*spirosta*-1 : 4-*diene*-3 : 11-*dione*, leaflets, m. p. 216°, $[\alpha]_D^{25}$ +30° (*c* 0·439), $\lambda_{max.}$ 239 mμ (log ε 4·12 in PrⁱOH) (Found: C, 64·1; H, 6·8; Br, 16·3. $C_{27}H_{35}O_4Br$ requires C, 64·4; H, 7·0; Br, 15·9%). The 3-(2 : 4-*dinitrophenylhydrazone*) formed red plates, m. p. 257—260° (decomp.), $\lambda_{max.}$ 389 mμ (log ε 4·49 in PrⁱOH) (Found: N, 8·0; Br, 11·6. $C_{33}H_{39}O_6N_4Br$ requires N, 8·4; Br, 12·0%).

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2α : 4α : 12α : 23ξ-*Tetrabromo*-5α : 25D-*spirostan*-3 : 11-*dione*, leaflets, m. p. 197—202°, $[\alpha]_D^{28}$ −70° (*c* 0·364) (Found: C, 43·6; H, 4·9; Br, 42·7. $C_{27}H_{36}O_4Br_4$ requires C, 43·6; H, 4·9; Br, 43·0%), after crystallisation from methylene chloride–methanol, was obtained by treating 12α : 23ξ-dibromo-5α : 25*D*-spirostan-3 : 11-dione (10 g.) in acetic acid (250 ml.) with bromine in acetic acid (31·7 ml. of 1·08M) with stirring during ½ hr. and then leaving the mixture overnight at room temperature.

23ξ-*Bromo*-25D-*spirost*-4-*en*-3 : 11-*dione* (IX; R′ = Br).—(*a*) 2α : 4α : 12α : 23ξ-Tetrabromo-5α : 25*D*-spirostan-3 : 11-dione (9·15 g.) in dry acetone (300 ml.) and sodium iodide (20 g.) were heated under reflux under nitrogen for 24 hr. The product was isolated with methylene chloride, dissolved in benzene (100 ml.) and acetic acid (50 ml.), and stirred with zinc dust (20 g.) for ½ hr. at room temperature. It was then chromatographed in benzene–light petroleum (200 ml.; 1 : 4) on alumina (100 g., B.D.H.). Elution with benzene–light petroleum (1 : 1) gave 2·35 g. of 23ξ-bromo-5α : 25*D*-spirostan-3 : 11-dione. Elution with benzene and benzene–ether (4 : 1) yielded 23ξ-*bromo*-25D-*spirost*-4-*en*-3 : 11-*dione*, needles, m. p. 217—219°, $[\alpha]_D^{26}$ +65° (*c* 0·742), $\lambda_{max.}$ 238 mμ (log ε 4·1 in EtOH) (Found: C, 64·2; H, 7·4; Br, 15·9. $C_{27}H_{37}O_4Br$ requires C, 64·1; H, 7·4; Br, 15·8%), after crystallisation from ethanol.

(*b*) 2α : 4α : 23ξ-Tribromo-5α : 25*D*-spirostan-3 : 11-dione (16·3 g.) and sodium iodide (33 g.) in dry acetone (330 ml.) were refluxed under nitrogen for 21 hr., The product, in benzene, was chromatographed on alumina (180 g.). Elution with benzene–light petroleum (1 : 1) gave 7 g. of (ultraviolet light) spectroscopically transparent material. Elution with benzene–ether gave the foregoing ketone, m. p. 216—219°, not depressed on admixture with a sample prepared as under (*a*).

25D-*Spirost*-4-*en*-3 : 11-*dione* (IX; R′ = H).—(*a*) 23ξ-Bromo-25*D*-spirost-4-en-3 : 11-dione (560 mg.) in acetic acid (12·5 ml.) containing sodium acetate (2·5 g.) was heated with zinc dust (2 g.) under reflux for 2 hr. 25D-*Spirost*-4-*en*-3 : 11-*dione*, isolated with benzene, formed plates, m. p. 212—215°, $[\alpha]_D^{26}$ +60° (*c* 0·568), $\lambda_{max.}$ 237 mμ (log ε 4·10 in EtOH) (Found: C, 76·4; H, 8·8. $C_{27}H_{38}O_4$ requires C, 76·1; H, 9·0%), from acetone–hexane.

(*b*) 23ξ-Bromo-25*D*-spirost-4-en-3 : 11-dione (1 g.) and sodium iodide (1 g.) in acetic acid (15 ml.) were heated under nitrogen on a steam-bath for 20 hr. The solution was poured into excess of sodium thiosulphate solution, and the product isolated with benzene and purified from acetone–hexane, to give 25*D*-spirost-4-en-3 : 11-dione, m. p. 211—215°, not depressed on admixture with a sample prepared as under (*a*).

2ξ : 6ξ - 23ξ-*Tribromo*-25D-*spirost*-4-*en*-3 : 11-*dione* (XII).—23ξ-Bromo-25*D*-spirost-4-en-3 : 11-dione (2 g.), suspended in dry ether (120 ml.), was treated dropwise with bromine in acetic acid (7·6 ml. of 1·05M) at 0—5°. After ½ hr. the ether was removed under reduced pressure at 20°, methanol (20 ml.) was added, and the separated solids were collected after ½ hr. Purification from methylene chloride–methanol gave 2ξ : 6ξ : 23ξ-*tribromo*-25D-*spirost*-4-*en*-3 : 11-*dione*, leaflets, m. p. 209—210°, $[\alpha]_D^{24}$ +8° (*c* 0·522), $\lambda_{max.}$ 236—237 mμ (log ε 4·0 in PrⁱOH) (Found: C, 49·5; H, 5·4; Br, 36·8. $C_{27}H_{35}O_4Br_3$ requires C, 48·9; H, 5·3; Br, 36·2%).

23ξ-*Bromo*-25D-*spirosta*-1 : 4 : 6-*triene*-3 : 11-*dione* (XI; R′ = Br).—The foregoing compound (1 g.) in collidine (10 ml.) was heated under reflux under nitrogen for 1¼ hr. The product, in benzene, was percolated through alumina (7 g.) and then purified from acetone–hexane, to give 23ξ-*bromo*-25D-*spirosta*-1 : 4 : 6-*triene*-3 : 11-*dione*, leaflets, m. p. 200—204°, $[\alpha]_D^{24}$ +51° (*c* 0·24), $\lambda_{max.}$ 225 (log ε 4·03), 269 (log ε 3·87) and 305 mμ (log ε 3·93) in PrⁱOH (Found: C, 61·7; H, 6·5; Br, 20·8. $C_{27}H_{33}O_4Br$ requires C, 64·6; H, 6·6; Br, 16·0%).

Debromination of 23ξ-*bromo*-25D-*spirosta*-1 : 4-*diene*-3 : 11-*dione with Zinc Dust*.—This dione (500 mg.) in acetic acid (10 ml.), sodium acetate (2 g.; anhyd.) and zinc dust (2 g.) were boiled under reflux for 1·5 hr. (cf. Cornforth *et al.*[2]). The product, isolated by means of ether, was a bromine-free gum which gave no crystalline material on chromatography over alumina (10 g.) and failed to form a 2 : 4-dinitrophenylhydrazone.

25D-*Spirosta*-1 : 4-*diene*-3 : 11-*dione* (VII; R′ = H), prepared by heating 23ξ-bromo-25*D*-spirosta-1 : 4-diene-3 : 11-dione (VII; R′ = Br) (5 g.) and sodium iodide (10 g.) in acetic acid (75 ml.) under nitrogen on a steam-bath for 30 hr., formed plates, m. p. 240—243°, $[\alpha]_D^{15}$ +36° (*c* 0·926), $\lambda_{max.}$ 238 mμ (log ε 4·15 in PrⁱOH) (Found: C, 76·1; H, 8·5. $C_{27}H_{36}O_4$ requires C, 76·4; H, 8·6%), after crystallisation from methylene chloride–methanol.

Reduction of Cholesta-1 : 4-*dien*-3-*one with Zinc and Acetic Acid*.—Cholesta-1 : 4-dien-3-one (1 g.) was reduced under reflux with zinc dust (2 g.) in acetic acid (10 ml.) containing sodium acetate (2 g.). The product, isolated with ether, was chromatographed in benzene on alumina

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(30 g.). Elution with light petroleum, followed by purification from the same solvent, yielded a *hydrocarbon*, m. p. 190—196°, $\lambda_{max.}$ 250 ($E^{1\%}_{1\,cm.}$ 116), 336 ($E^{1\%}_{1\,cm.}$ 264) and 352 mμ ($E^{1\%}_{1\,cm.}$ 265) in hexane (Found : C, 87·8; H, 11·5%).

3β-*Acetoxy*-12 : 12-*ethylenedioxy*-5α-*pregnan*-20-*one* (X).—Finely powdered 3β-acetoxy-5α-pregnane-12 : 20-dione (82 g.) in freshly distilled ethylene glycol (600 ml.) was treated with boron trifluoride–ether complex (120 ml.) for 72 hr. at room temperature with occasional swirling. The product, in pyridine (200 ml.), was treated overnight at room temperature with acetic anhydride (500 ml.) and recovered in benzene and crystallised from methanol. 3β-*Acetoxy*-12 : 12-*ethylenedioxy*-5α-*pregnan*-20-*one* formed leaflets, m. p. 159—162°, $[\alpha]_D^{25}$ +99° (*c* 0·624) (Found : C, 72·4; H, 8·9. $C_{25}H_{36}O_5$ requires C, 71·8; H, 9·1%), after crystallisation from methanol.

12 : 12-*Ethylenedioxy*-5α-*pregnane*-3β : 20ξ-*diol* (XIII), prepared by reducing the foregoing compound (14·8 g.) in methanol (1·5 l.) with sodium hydroxide (7·5 g.) and sodium borohydride (3 g.) in 50% aqueous methanol (300 ml.) at room temperature for 60 hr., formed prisms, m. p. 198—200°, $[\alpha]_D^{25}$ +40° (*c* 1·060) (Found : C, 73·2; H, 10·0. $C_{23}H_{38}O_4$ requires C, 73·0; H, 10·1%), from acetone.

3β : 20ξ-*Dihydroxy*-5α-*pregnan*-12-*one* (XIV; R = R′ = H), prepared by heating the foregoing compound (22·5 g.) in 90% acetic acid (450 ml.) on the steam-bath for 1 hr., formed rectangular plates, m. p. 230—233°, $[\alpha]_D^{25}$ +91° (*c* 0·701) (Found : C, 75·3; H, 10·4. $C_{21}H_{34}O_3$ requires C, 75·4; H, 10·2%), from methylene chloride–ethyl acetate.

Acetylation of the foregoing compound (28·4 g.) in pyridine (200 ml.) with acetic anhydride (100 ml.) at room temperature overnight gave 3β-*acetoxy*-20ξ-*hydroxy*-5α-*pregnan*-12-*one*, prisms, m. p. 198—201°, $[\alpha]_D^{22}$ +71° (*c* 0·485) (Found : C, 73·8; H, 9·7. $C_{23}H_{36}O_4$ requires C, 73·5; H, 9·6%), after crystallisation from acetone–hexane. The mother-liquors were taken to dryness and the residue extracted several times with light petroleum under reflux. The insoluble fraction yielded a further quantity of the 3-monoacetate. The soluble fraction, after purification from aqueous methanol, yielded 3β : 20ξ-*diacetoxy*-5α-*pregnan*-12-*one*, leaflets, m. p. 135—138°, $[\alpha]_D^{26}$ +96° (*c* 0·576) (Found : C, 71·6; H, 8·9. $C_{25}H_{38}O_5$ requires C, 71·7; H, 9·1%). The last compound formed the sole product when the diol (1 g.) in acetic anhydride (5 ml.) and pyridine (3 ml.) was heated on the steam-bath for 16 hr.

3β-*Acetoxy*-11α-*bromo*-20ξ-*hydroxy*-5α-*pregnan*-12-*one*.—3β-Acetoxy-20ξ-hydroxy-5α-pregnan-12-one (10 g.) in acetic acid (400 ml.) at 30° was treated with 3 drops of a 50% solution of hydrogen bromide in acetic acid, followed by bromine in acetic acid (24·5 ml. of 1·1M), added dropwise over 30 min. After a further 10 min. the product was isolated with methylene chloride and purified from ethyl acetate. 3β-*Acetoxy*-11α-*bromo*-20ξ-*hydroxy*-5α-*pregnan*-12-*one* formed prisms, m. p. 164—167°, $[\alpha]_D^{22}$ +12° (*c* 0·412) (Found : C, 61·0; H, 7·9; Br, 17·5. $C_{23}H_{35}O_4Br$ requires C, 60·7; H, 7·8; Br, 17·5%).

11β : 12β-*Epoxy*-5α-*pregnane*-3β : 20ξ-*diol* (XV).—The 11α-bromo-ketone (6 g.) in ethanol (900 ml.) was treated with sodium hydrogen carbonate (600 mg.) and sodium borohydride (600 mg.) in water (30 ml.) for 2 hr. with stirring. Potassium hydroxide (9 g.) was then added and stirring continued for 4 hr. The product, 11β : 12β-*epoxy*-5α-*pregnane*-3β : 20ξ-*diol*, m. p. 218—221°, $[\alpha]_D^{24}$ +34° (*c* 0·745), crystallised from aqueous methanol (Found : C, 75·6; H, 10·3. $C_{21}H_{34}O_3$ requires C, 75·4; H, 10·2%).

12α-*Bromo*-5α-*pregnane*-3β : 11β : 20ξ-*triol* (XVI; R = H), needles, m. p. 210—211°, $[\alpha]_D^{26}$ +29° (*c* 0·448 in EtOH) (Found : C, 60·9; H, 8·4; Br, 19·1. $C_{21}H_{35}O_3Br$ requires C, 60·7; H, 8·5; Br, 19·2%), after crystallisation from aqueous methanol, was prepared by treating the foregoing compound (3·4 g.) in dioxan (70 ml.) with 48% hydrobromic acid (5 ml.) in dioxan (10 ml.) and leaving the mixture at room temperature overnight. The *diacetate* separated from methylene chloride–methanol in flattened rods, m. p. 216—218°, $[\alpha]_D^{23}$ +54° (*c* 0·664) (Found : C, 59·8; H, 7·6; Br, 16·3. $C_{25}H_{39}O_5Br$ requires C, 60·1; H, 7·9; Br, 16·0%).

12α-*Bromo*-5α-*pregnane*-3 : 11 : 20-*trione* (XVII; R = Br).—The foregoing compound (2 g.) in methylene chloride (30 ml.) was treated below 25° with vigorous stirring with chromic acid (3 g.) in water (12 ml.) and acetic acid (12 ml.) during ½ hr. Stirring was maintained for a further 4½ hr., after which the product was isolated with methylene chloride and purified from aqueous acetone. The *trione* formed thick needles, m. p. 178—180°, $[\alpha]_D^{25}$ +2° (*c* 0·889) (Found : C, 61·9; H, 7·1; Br, 19·3. $C_{21}H_{29}O_3Br$ requires C, 61·6; H, 7·1; Br, 19·5%).

5α-Pregnane-3 : 11 : 20-trione (XVII; R = H), m. p. 216—218°, alone or on admixture with an authentic sample, $[\alpha]_D^{23}$ +133° (*c* 0·748) (Found : C, 76·5; H, 9·1. Calc. for $C_{21}H_{30}O_3$:

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C, 76·3; H, 9·1%), was prepared by stirring the foregoing compound (6·25 g.) in benzene (60 ml.) and acetic acid (100 ml.) with zinc dust (10 g. added in 3 portions at intervals of ½ hr.) for a total of 1 hr.

Pregna-1 : 4 : 16-*triene*-3 : 11 : 20-*trione* (XVIII).—The foregoing compound (1·5 g.) in acetic acid (50 ml.) was treated dropwise with bromine in acetic acid (13 ml.; 1·05M). After 20 hr. at room temperature the product was isolated with ether and then heated under reflux with collidine for 1½ hr. under nitrogen. The resulting material, in benzene–light petroleum, was chromatographed on alumina (16 g.). After elution with benzene–light petroleum, elution with benzene and benzene–ether (1 : 1) gave *pregna*-1 : 4 : 16-*triene*-3 : 11 : 20-*trione*, yellow leaflets, m. p. 237—241°, $[\alpha]_D^{25}$ +23° (*c* 0·644), $\lambda_{max.}$ 236 mμ (log ε 4·38 in EtOH) (Found : C, 77·2; H, 7·5. $C_{21}H_{24}O_3$ requires C, 77·7; H, 7·5%), after crystallisation from acetone–hexane.

The 3 : 20-*bis*-(2 : 4-*dinitrophenylhydrazone*) formed plates, m. p. 190°, $\lambda_{max.}$ 385—386 mμ (log ε 4·7 in EtOH) (Found : N, 15·8; $C_{33}H_{32}O_9N_8$ requires N, 16·4%).

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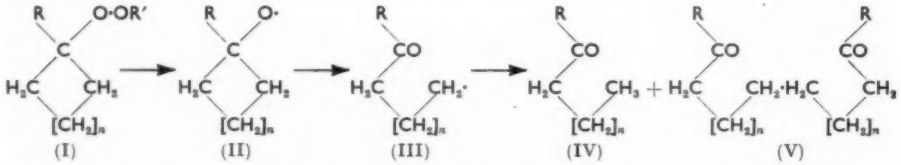
206. *The Decomposition of* 1-*Phenylcyclohexyl Peroxides.*

By D. H. HEY, C. J. M. STIRLING, and GARETH H. WILLIAMS.

1-Phenyl*cyclo*hexyl hydroperoxide and di-(1-phenyl*cyclo*hexyl) peroxide have been prepared. The thermal decomposition of di-(1-phenyl*cyclo*hexyl) peroxide in chlorobenzene and in pyridine gave *n*-pentyl phenyl ketone, 1 : 10-dibenzoyldecane, and an unidentified ketone, m. p. 104·5°. The thermal decomposition of the hydroperoxide in chlorobenzene gave *n*-pentyl phenyl ketone, but on treatment with aqueous ferrous sulphate it gave 1 : 10-dibenzoyldecane.

HAWKINS,[1] in a study of the thermal decomposition of 1-methyl*cyclo*pentyl and 1-methyl-*cyclo*hexyl hydroperoxide, obtained products consistent with the formation of the radicals (II and III; R = Me, R′ = H; *n* = 2 and 3 respectively). Hawkins and Young [2] showed that 1-methyl*cyclo*pentyl hydroperoxide reacts with ferrous sulphate to give dodecane-2 : 11-dione (V; R = Me; *n* = 2), which was considered to arise by the dimerisation of the radical (III; R = Me; *n* = 2). Corresponding results were obtained with 1-methyl*cyclo*hexyl hydroperoxide. It was clear, therefore, that oxygen–oxygen fission of the hydroperoxide to give the radical (II) was followed by ring-scission and rearrangement to give the radical (III).

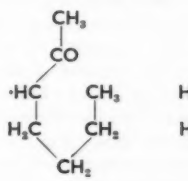


Earlier, Chavanne and his co-workers [3] had found that the autoxidation of substituted *cyclo*pentanes and *cyclo*hexanes, among them 1-phenyl*cyclo*pentane, yielded open-chain oxygenated products of the same type as those obtained by Hawkins. Although it is possible that hydroperoxides were formed initially in these reactions, no direct evidence of their presence was reported.

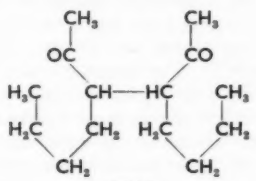
[1] Hawkins, *J.*, 1950, 2801.
[2] Hawkins and Young, *J.*, 1950, 2804.
[3] For references see Hawkins, *Quart. Rev.*, 1950, **4**, 251.

No study of the thermal decomposition of tertiary alicyclic peroxides in which the exocyclic group R is aryl has yet been made. In principle, it is possible for a radical of type (II) to break down in two ways: (*a*) by ring scission with the formation of a ketonic radical as above, or (*b*) by elimination of the group R with the formation of a cyclic ketone. In the present communication, an investigation of the decomposition of 1-phenyl*cyclo*hexyl hydroperoxide (I; R = Ph, R′ = H; $n = 3$) and di-(1-phenyl*cyclo*hexyl) peroxide (I; R = Ph, R′ = 1-phenyl*cyclo*hexyl; $n = 3$), in which phenyl radicals may be formed by mechanism (*b*), is reported. Neither di-(1-phenyl*cyclo*hexyl) peroxide nor the hydroperoxide has previously been prepared in a pure state, although the autoxidation of 1-phenyl*cyclo*hexane has been reported [4,5] to give a product which contained 18% of 1-phenyl*cyclo*hexyl hydroperoxide. Some confusion, however, exists as to whether a pure product can be obtained from this reaction, but in neither case were the properties of the hydroperoxide reported. In the present work, attempts to prepare 1-phenyl*cyclo*hexyl hydroperoxide by the reaction of 1-phenyl*cyclo*hexanol with 30% hydrogen peroxide and sulphuric acid failed. It was, however, obtained in 75% yield from 1-phenyl*cyclo*hexanol by the general method described by Davies, Foster, and White.[6] Di-(1-phenyl*cyclo*hexyl) peroxide was prepared in low yield by condensation of the hydroperoxide with 1-phenyl*cyclo*hexanol in the presence of a catalytic quantity of toluene-*p*-sulphonic acid.[7]

The thermal decomposition of di-(1-phenyl*cyclo*hexyl) peroxide in chlorobenzene and in pyridine yielded *n*-pentyl phenyl ketone (37% and 21% respectively) together with two solid ketones which melted at 97° and 104·5°. The former was identified by comparison with an authentic synthetic specimen as 1 : 10-dibenzoyldecane, but the ketone of m. p. 104·5° was not identified. Milas and Perry [8] isolated 3 : 4-di-*n*-butylhexane-2 : 5-dione (VII) from the decomposition products of *tert.*-butyl-1-methyl*cyclo*hexyl peroxide (I; R = Me, R′ = Bu^t; $n = 3$). This product was considered to arise by rearrangement of the radical (II; R = Me; $n = 3$), produced by the initial homolysis, to give the radical (VI), which then dimerised. The unknown ketone obtained in the present investigation, however, failed to give a pyrrole derivative on treatment with ammonium acetate and glacial acetic acid.[9] This compound is therefore probably not a 1 : 4-diketone analogous to (VII).



(VI)



(VII)

The decomposition of 1-phenyl*cyclo*hexyl hydroperoxide in chlorobenzene gave *n*-pentyl phenyl ketone, but neither of the solid ketones obtained from the experiments with the symmetrical peroxide could be isolated. Treatment of the hydroperoxide with ferrous sulphate by Hawkins and Young's procedure,[2] however, gave 1 : 10-dibenzoyldecane in 22% yield. None of the ketone, m. p. 104·5°, was isolated from this reaction.

In the experiments on the thermal decomposition of di-(1-phenyl*cyclo*hexyl) peroxide and of the hydroperoxide in chlorobenzene and pyridine, no evidence was obtained for the formation of derivatives of diphenyl or phenylpyridine, and it is clear that elimination of a phenyl radical from the 1-phenyl*cyclo*hexyloxy-radical (II; R = Ph; $n = 3$), which is initially produced, does not occur. In addition, *cyclo*hexanone could not be detected in

[4] Monsanto Ltd., B.P. 681,613.
[5] Rhone-Poulenc Ltd., B.P. 712,264.
[6] Davies, Foster, and White, *J.*, 1953, 1541.
[7] Hercules Powder Co., U.S.P. 2,668,180.
[8] Milas and Perry, *J. Amer. Chem. Soc.*, 1946, **68**, 1938.
[9] Kapf and Paal, *Ber.*, 1888, **21**, 3053.

the products and its absence confirms that cleavage of the bond between the aromatic nucleus and the *cyclo*hexane ring does not take place. This preferential cleavage of the alicyclic ring is clearly due to the considerable loss of the resonance energy arising from the conjugation of the carbonyl group with the aromatic nucleus, which would be involved in the disruption of the radical (II) by mechanism (*b*). It is evident, therefore, that the decomposition of the 1-phenyl*cyclo*hexyl peroxides follows the pattern observed by Hawkins and Young with the methyl analogues. The radical (II; R = Ph; $n = 3$) undergoes ring scission to give the radical (III; R = Ph; $n = 3$). This radical then either disproportionates or abstracts hydrogen from the peroxide or a subsequent decomposition product with the formation of the main product, *n*-pentyl phenyl ketone (IV; R = Ph; $n = 3$). Dimerisation of the same radical yields 1 : 10-dibenzoyldecane. Disproportionation of the radical (III; R = Ph; $n = 3$) would lead to the formation of unsaturated products which, on subsequent attack by other radicals, would give polymers. This may explain the formation of the high-boiling intractable residues (60—70%) that are encountered in these reactions.

Experimental

All solids were crystallised to constant m. p. The light petroleum used had b. p. 40—60°.

1-*Phenyl*cyclo*hexyl Hydroperoxide*.—A suspension of 1-phenyl*cyclo*hexanol [10] (7·3 g.) in ether (10 ml.) was added to a solution of concentrated sulphuric acid (0·04 ml.) in 86% hydrogen peroxide (10 ml.). The mixture was stirred for 6 hr. at room temperature, and water (50 ml.) was then added and the organic layer separated. The aqueous layer was extracted with ether (2 × 25 ml.), and the combined ethereal solutions were extracted with saturated aqueous sodium hydrogen carbonate (2 × 25 ml.), washed with water, and after being dried (Na_2SO_4), were allowed to evaporate at room temperature. The residue (7·6 g.), after crystallisation from light petroleum, gave 1-*phenyl*cyclo*hexyl hydroperoxide* (6 g.) in long white needles, m. p. 60° (Found: C, 74·5; H, 8·3. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%). Treatment of the product with 15% sulphuric acid (cf. ref. 4) gave *cyclo*hexanone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 159—160°) and phenol (phenyl benzoate, m. p. and mixed m. p. 68°).

Di-(1-*phenyl*cyclo*hexyl*) *Peroxide*.—1-Phenyl*cyclo*hexanol (1·5 g.) and 1-phenyl*cyclo*hexyl-hydroperoxide (0·8 g.) were heated together at 80°. A small crystal of toluene-*p*-sulphonic acid was added to the molten mixture which was maintained at 80° for 5 hr. Methanol (20 ml.) was added and the solid which separated was crystallised from ethanol to give *di*-(1-*phenyl*cyclo*hexyl*) *peroxide* (0·35 g.) in needles, m. p. 123—124° (Found: C, 81·5; H, 8·65. $C_{24}H_{30}O_2$ requires C, 82·2; H, 8·6%). The infrared spectrum showed a strong absorption band at 902 cm.$^{-1}$. Absorption in this region is regarded as being characteristic of the peroxide linkage.[11] Preparation on a larger scale gave considerably lower yields.

1 : 10-*Dibenzoyldecane*.—Decane-1 : 10-dicarboxylic acid (5 g.) was heated under reflux with thionyl chloride (20 ml.) until the evolution of gases ceased. The excess of thionyl chloride was removed under reduced pressure and the pale yellow residue of the acid chloride, dissolved in dry benzene (25 ml.), was added dropwise, with cooling, during 45 min. to a vigorously stirred suspension of aluminium chloride (10 g.) in dry benzene (30 ml.). The mixture was heated to 80° during 30 min. and kept at 80° until no further hydrogen chloride was evolved. After cooling, the mixture was poured on crushed ice (200 g.) and concentrated hydrochloric acid (40 ml.), and chloroform (100 ml.) was added. The organic layer was separated, washed with 10% aqueous potassium hydroxide (2 × 50 ml.), and dried (Na_2SO_4). Chloroform and benzene were distilled off, and addition of light petroleum to the residue then gave a white solid (4·8 g.), m. p. 95°. One crystallisation from benzene–light petroleum gave 1 : 10-*dibenzoyldecane* as plates, m. p. 96—97° (Found: C, 82·0; H, 8·4. $C_{24}H_{30}O_2$ requires C, 82·2; H, 8·6%).

Decomposition of Di-(1-*phenyl*cyclo*hexyl*) *Peroxide*.—(a) *In chlorobenzene*. A solution of di-(1-phenyl*cyclo*hexyl) peroxide (4 g.) in anhydrous chlorobenzene (100 ml.) was boiled under reflux for 6 days. The dark red mixture, when cold, was extracted with 10% aqueous sodium hydroxide (50 ml.) and with saturated aqueous sodium hydrogen sulphite (50 ml.). After being washed with water and dried (Na_2SO_4), the mixture was distilled to remove chlorobenzene, and

[10] Sabatier and Mailhe, *Compt. rend.*, 1904, **138**, 1322.
[11] Bellamy, "Infra-red Spectra of Complex Molecules," Methuen, London, 1954.

subsequent distillation of the residue gave a pale yellow oil (1·5 g.), b. p. 126°/10 mm., which solidified at 0°, and a residue (2·14 g.), b. p. above 200°/10 mm. The oil contained chlorine (3·5%. Calc. for $C_{12}H_9Cl$: Cl, 18·9%) attributed to traces of residual solvent (cf. the next experiment), and gave a semicarbazone, m. p. 130°, and a 2 : 4-dinitrophenylhydrazone, which after chromatography in benzene on alumina had m. p. 165°. Schroeter [12] reports b. p. 145°/22 mm. for *n*-pentyl phenyl ketone and m. p. 132° for its semicarbazone, but Fahim and Mustapha [13] report *n*-pentyl phenyl ketone as giving a 2 : 4-dinitrophenylhydrazone m. p. 129°. An authentic specimen of *n*-pentyl phenyl ketone (b. p. 140°/15 mm.) was prepared by Schroeter's method and gave a semicarbazone, m. p. 130°, and a 2 : 4-dinitrophenylhydrazone, m. p. 167° (Found : N, 15·3. Calc. for $C_{18}H_{20}O_4N_4$: N, 15·7%). The m. p.s of these derivatives were not depressed on admixture with the corresponding derivatives prepared from the product obtained from the decomposition of the peroxide. The residue, on treatment with light petroleum (80 ml.), yielded a white solid (0·4 g.), m. p. 88—92°. This material consisted of two compounds, one of which crystallised in plates, and the other as rhombs. When these were separated manually, the former had m. p. 92—95°, undepressed on admixture with 1 : 10-dibenzoyldecane, and the latter had m. p. 102—103°, depressed on admixture both with the former compound and with di-(1-phenyl*cyclo*hexyl) peroxide, but gave a precipitate with Brady's reagent. Neither compound could be further purified. Evaporation of the light petroleum mother-liquors yielded an intractable gum. The sodium hydroxide and sodium hydrogen sulphite extracts were acidified with hydrochloric acid and extracted with ether, but evaporation of the extracts in each case yielded only traces of dark products which could not be identified.

(b) *In pyridine.* A solution of di-(1-phenyl*cyclo*hexyl) peroxide (11 g.) in anhydrous pyridine (150 ml.) was boiled under reflux for 2 weeks. The bulk of the solvent was distilled off and chloroform (100 ml.) was added to the dark residue. The solution was extracted with 5N-hydrochloric acid (4 × 25 ml.), washed with water, and dried (Na_2SO_4). The acid extracts were made alkaline with potassium hydroxide and extracted with benzene (5 × 30 ml.). The benzene extracts, after being dried ($CaCl_2$), were distilled. The sole product, however, was a dark tar (0·2 g.), b. p. above 200°/20 mm. The chloroform solution was concentrated and distilled to give a pale yellow oil (2·3 g.), b. p. 148°/22 mm., and a residue (9 g.). The oil gave a semicarbazone, m. p. 130°, and a 2 : 4-dinitrophenylhydrazone, m. p. 166·5°, which did not depress the m. p.s of the corresponding derivatives of *n*-pentyl phenyl ketone. Treatment of the residue with light petroleum gave a white solid (1·1 g.), m. p. 88—92°. A portion of this solid (0·8 g.) was dissolved in benzene (20 ml.) and was poured on an alumina column (25 × 2 cm.). Elution with light petroleum–benzene afforded prisms (0·36 g.) which, after crystallisation from methanol, had m. p. 104·5°, undepressed on admixture with the *substance*, m. p. 102—103°, obtained in the experiment with chlorobenzene (Found : C, 82·7; H, 8·8. $C_{26}H_{34}O_2$ requires C, 82·6; H, 9·0%). The ketone, m. p. 104·5° (0·2 g.), was added to a solution of ammonium acetate (10 g.) in glacial acetic acid (25 ml.) and the mixture was boiled under reflux for 16 hr. The cold mixture was made alkaline with sodium carbonate and was extracted with ether (3 × 30 ml.). The extracts, after being dried (Na_2SO_4), were evaporated to dryness but the dark residue did not contain nitrogen and gave no distinct colour with sulphuric acid. Elution of the column was continued with 1 : 1 benzene–ether to give white plates (0·18 g.), m. p. 96—97°, undepressed on admixture with 1 : 10-dibenzoyldecane. The light petroleum mother-liquors were poured on an alumina column (25 × 2 cm.), and elution with benzene (100 ml.) gave a brown oil (3·7 g.) which, on the addition of methanol (25 ml.), gave a white solid (0·5 g.). Crystallisation of the solid from methanol gave the ketone obtained from the previous chromatography, m. p. and mixed m. p. 104·5°.

Decomposition of 1-*Phenyl*cyclo*hexyl Hydroperoxide in Chlorobenzene.*—1-Phenyl*cyclo*hexyl hydroperoxide (5 g.) in anhydrous chlorobenzene (150 ml.) was boiled under reflux. Decomposition was complete in 60 hr. (negative starch–iodide test) and the cold mixture was extracted successively with 10% aqueous sodium hydroxide (2 × 50 ml.) and with saturated aqueous sodium hydrogen sulphite (2 × 75 ml.). The solution was washed with water and, after being dried (Na_2SO_4), was distilled to remove chlorobenzene. Distillation of the residue gave a yellow oil (2·3 g.), b. p. 126°/8 mm., and a residue (0·7 g.). The oil gave a 2 : 4-dinitrophenylhydrazone (m. p. 158°, from benzene–ethanol), which could not be further purified but

[12] Schroeter, *Ber.*, 1907, **40**, 1589.
[13] Fahim and Mustapha, *J.*, 1949, 519.

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did not depress the m. p. of *n*-pentyl phenyl ketone 2 : 4-dinitrophenylhydrazone. A semicarbazone could not be prepared. No pure product could be obtained either from the residue or from the sodium hydroxide or sodium hydrogen sulphite extracts.

Reaction of 1-*Phenylcyclohexyl Hydroperoxide with Ferrous Sulphate.*—A saturated ethanolic solution of 1-phenyl*cyclo*hexyl peroxide (4 g.) was slowly added with shaking to a solution of ferrous sulphate (30 g.) in water (70 ml.). An exothermic reaction ensued, which was accompanied by a darkening of the mixture and precipitation of a brown solid. After 2 hr., the mixture was heated to 100° and the solid was dissolved by the addition of 10% sulphuric acid. The solution, when cold, was extracted with methylene chloride (2 × 50 ml.), and the extracts were washed with water and dried (Na_2SO_4). Methylene chloride was distilled off. Addition of methanol (30 ml.) to the residue (3 g.) precipitated 1 : 10-dibenzoyldecane (0·9 g.) which, after crystallisation from benzene–light petroleum, had m. p. and mixed m. p. 96—97°.

Thanks are accorded to Dr. R. H. Hall, of the Distillers Company Limited, for valuable advice on the preparation of the peroxide and hydroperoxide, to Messrs. Laporte Ltd., Luton, for the gift of 86% hydrogen peroxide, and to the Department of Scientific and Industrial Research for the award of a maintenance allowance (to C. J. M. S.).

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207. *The Photodecomposition of Carbon Dioxide and of Ammonia by Xenon* 1470 Å *Radiation.*

By H. JUCKER and ERIC K. RIDEAL.

The photochemical decomposition of carbon dioxide and of ammonia has been examined by the 1470 Å xenon radiation. The quantum efficiencies were found to be 1·9 ± 0·2 and 0·45 ± 0·1 molecule/quantum, respectively. The carbon dioxide decomposition is found to follow the scheme $CO_2 + h\nu \longrightarrow CO_2^*$; $CO_2^* + CO_2 \longrightarrow 2CO + O_2$. Atomic oxygen is not present. The decomposition of ammonia proceeds through the formation of NH_2 radicals, and the resulting hydrazine is photochemically decomposed.

OWING to the difficulties due to absorption inherent in radiation experiments with ultraviolet light of very short wavelength, little precise work has been published in this field. By the construction of a simple but novel xenon lamp these difficulties have been greatly reduced and it was decided to investigate the photolysis of gaseous carbon dioxide and of ammonia. According to Groth [1] carbon dioxide is decomposed photochemically into carbon monoxide and atomic oxygen. The energy required for the reaction

$$CO_2 \longrightarrow CO + O$$

is about 5·5 ev (corresponding to $\lambda \sim 2200$ Å). Carbon dioxide however only absorbs light in the extreme ultraviolet region commencing at *ca.* 1700 Å. Groth [2] evaluated the yield per quantum as nearly 1; but other investigators [3,4] have obtained either 1 or 1·5, atomic oxygen being produced in the reaction.

For the photolysis of ammonia Kuhn [5] found a quantum yield of 0·19 but other experiments lead to quantum yields between 0·5 and 11·0 for different pressures, light intensities, and temperatures.[6-9] Hydrazine was first detected among the products by Koenig and

[1] Groth, *Z. phys. Chem.*, 1937, *B*, **37**, 307, 315.
[2] *Idem, ibid.*, 1938, *B*, **38**, 366.
[3] Noyes and Leighton, "The photochemistry of gases," Reinhold, New York, 1941.
[4] Harris, and Kaminsky, *J. Amer. Chem. Soc.*, 1935, **57**, 1154.
[5] Kuhn, *Compt. rend.*, 1924, **177**, 956, 123.
[6] Wijnen and Taylor, *J. Chem. Phys.*, 1953, **21**, 233.
[7] Harteck and Oppenheimer, *Z. phys. Chem.*, 1932, *B*, **16**, 77.
[8] Ogg, Leighton, and Bergstrom, *J. Amer. Chem. Soc.*, 1934, **56**, 318.
[9] Wigg and Kistiakowsky, *ibid.*, 1932, **54**, 1836.

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Brings,[10] and this was likewise found in the presence of mercury in a streaming system by Gedye and Rideal.[11] Hydrazine when formed can again undergo decomposition.

Experimental

The lamp and reaction vessel are depicted in Fig. 1. The lamp consists of a quartz tube with one end electrode and one side electrode, each made of heavy tungsten rod containing barium thorate as electron-emitting material; each electrode is wrapped with a tungsten wire spiral. They are sealed in with molybdenum seals. The side electrode is protected from

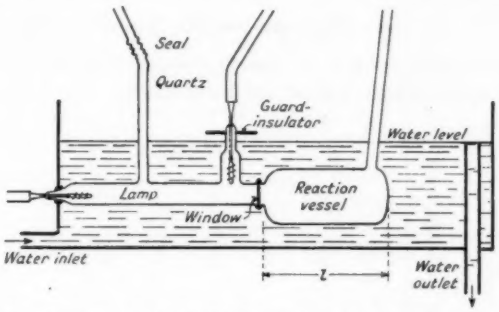

Fig. 1. *Lamp and reaction vessel.*

shorting by a round guard insulator. To the open end of the lamp is sealed by means of picein wax a fluorite window, 22 mm. in diameter and 1 mm. thick, which also acts as the radiation entry into the reaction vessel (length, *l*, 63 mm.); the whole assembly can be immersed in a constant-temperature water-bath. Both lamp and reaction vessel are connected to vacuum pumping lines, gas reservoirs, and a two-range McLeod guage.

For cleaning the lamp and degassing the electrodes the lamp is run in argon which is renewed from time to time. Impurities are gradually deposited on the window and there is a slow but steady decrease in intensity. In consequence frequent calibrations of the lamp were made by means of a Cambridge Instrument Co. thermocouple of 2 cm.^{2} area mounted in the reaction vessel itself and run when the latter was evacuated. The data were plotted on an " ageing " curve. The thermocouple was tested and calibrated by means of a standard lamp provided by the National Physical Laboratory. The xenon lamp is operated directly on the a.c. mains circuit and is brought into operation by means of a high-tension Tesla coil.

The characteristic current consumption with the lamp filled to 100 mm. pressure with xenon was: maximum current 20 A, 51·0 V; usual running conditions 12 A, 36·0 V; minimum running current 4·5 A, 24·5 V. The output of 1470 Å radiation at 12 A and 36·0 V was found by means of the thermocouple to be $1{\cdot}40 \times 10^{17}$ quanta/sec.

Helium and xenon were supplied by the British Oxygen Company. The other gases were prepared and purified in the usual manner.

During the period of radiation the gas pressure was continuously recorded and analysis performed by fractionation with liquid air.

Results

(a) *Carbon Dioxide.*—In Fig. 2 the initial rate of decomposition for constant light flux is plotted against pressure. As might be expected a plot of the log of the initial decomposition rate against the reciprocal of the pressure (Fig. 3) gives a linear relation in accordance with Lambert's law. A very definite falling off in the rate is noted at very low pressures. The quantum yield is $1{\cdot}9 \pm 0{\cdot}2$ molecules/quantum. This suggests that the reaction mechanism is:

$$CO_2^* + h\nu \longrightarrow CO_2^*$$
$$CO_2^* + CO_2 \longrightarrow 2CO + O_2$$

and that contrary to the previous view atomic oxygen is not formed in the process.

[10] Koenig and Brings, *Z. phys. Chem., Bodenstein-Festband*, 1931, 541.
[11] Gedye and Rideal, *J.*, 1932, 1166.

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The photochemical yield, as determined by change in pressure, rapidly decreases with time.

To investigate whether atomic oxygen is formed or not as a result of the primary act, hydrogen in various proportions was added to the carbon dioxide, the latter being maintained at a constant pressure of 100 mm. As is indicated in Fig. 4 the pressure does not remain constant, but even with a large excess of hydrogen a slight increase of pressure is still obtained.

The products of the reaction, carbon monoxide and oxygen, can undergo further photochemical reactions. These include:

$$O_2 + h\nu \longrightarrow 2O;\ O + O + \text{wall} \longrightarrow O_2;\ O + O_2 \longrightarrow O_3$$

The reaction $CO + O \longrightarrow CO_2$ requires, according to Jackson,[12] more activation energy than the others and is thus less probable.

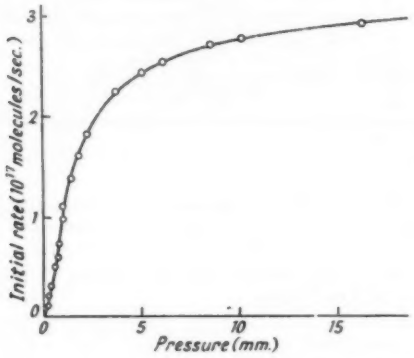


FIG. 2. *Initial rate of decomposition of carbon dioxide at different pressures.*

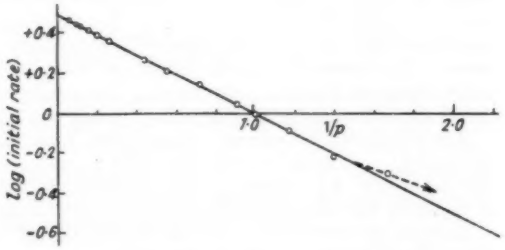


FIG. 3. *Plot of the logarithm of the initial rate of decomposition of carbon dioxide against the reciprocal of the pressure.*

The other possible reaction, $CO + h\nu \longrightarrow CO^*$, should, in the presence of hydrogen, result in the formation of formaldehyde [7], $CO^* + H_2 \longrightarrow CH_2O$, which indeed was found by freezing out the condensable gases and testing the condensate with sodium sulphite. The formaldehyde formed does not accumulate in the system as it decomposes by the mechanism

$$CH_2O + h\nu \longrightarrow HCO + H$$

and

$$CHO \longrightarrow H + CO$$

The atomic hydrogen formed in these secondary reactions can react with carbon dioxide to form formaldehyde, although as Lewis [13] showed the yield is somewhat small, as well as with the oxygen to form water. Thus no pressure change is to be expected.

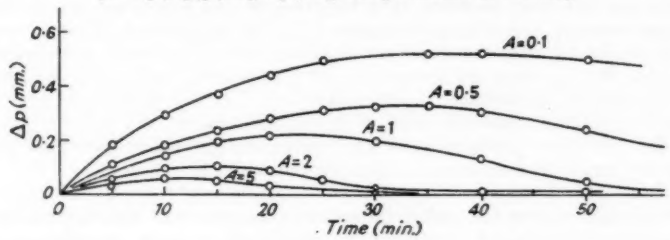
Further experiments were carried out with the lamp containing argon where the 1870 Å radiation is not absorbed by carbon monoxide. The form of the decomposition

[12] Jackson, *J. Amer. Chem. Soc.*, 1934, **56**, 2631.
[13] Lewis, *ibid.*, 1928, **50**, 27.

yield–time curves were substantially the same as with the xenon radiation but with considerably reduced slope since with the elimination of the carbon monoxide secondary reactions, carbon monoxide not being excited by this radiation, the back reactions are considerably reduced.

(b) *Ammonia.*—In Fig. 5 is plotted the decomposition rate–time curve for the photochemical decomposition of ammonia. The initial decomposition rate only obeys Lambert's law for medium pressures. At high pressures complete absorption of the radiation takes place. Under these conditions the quantum yield is $0{\cdot}45 \pm 0{\cdot}1$ molecule/quantum.

FIG. 4. *Pressure change (Δp) with time on irradiation of carbon dioxide–hydrogen mixtures.* [A = $p(H_2)/p(CO_2)$; $p(CO_2)$ being constant at 10 mm.]



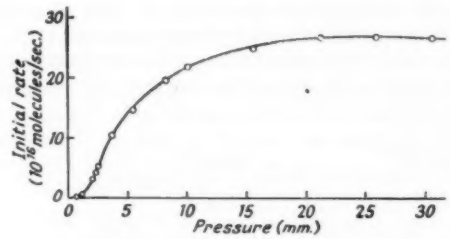


FIG. 5. *Initial rate of decomposition of ammonia at different pressures.*

It seemed probable that the primary photochemical reaction is a scission of the molecule to yield atomic hydrogen and NH_2 radicals:

$$NH_3 + h\nu \longrightarrow NH_2 + H$$

Hydrazine could readily be detected after a few minutes by cooling the trap to $-20°$ and then examining the contents.

The small observable rate of reaction at low pressures supports the view that the NH_2 radicals are adsorbed on the walls before hydrazine formation ($NH_2 + NH_2 \longrightarrow N_2H_4$) reaches a steady state. The presence of atomic hydrogen is readily established by the rapid formation of water on the addition of oxygen to the reacting gas.

The hydrazine formed reaches a stationary state by undergoing a secondary photochemical decomposition [14] to nitrogen and hydrogen. Here it appears that 2 quanta are involved, since 4 quanta are required to effect the decomposition of two molecules of

$$2N_2H_4 + 2h\nu \longrightarrow N_2 + 3H_2$$

ammonia into its final products, hydrogen and nitrogen.

Our thanks are due to Mr. E. H. Nelson of the General Electric Co. for fabrication of the lamp, to the Ramsay Trustees for the award of a Ramsay Fellowship (Swiss) to one of us (H. J.), and to the Monsanto Chemical Co. for financial assistance.

KING'S COLLEGE, LONDON.
IMPERIAL COLLEGE, LONDON.

[*Received, May 1st,* 1956.]

[14] Wenner and Beckman, *J. Amer. Chem. Soc.*, 1932, **54**, 2787.

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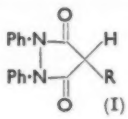
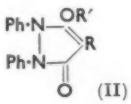
208. 3 : 5-*Dioxo*-1 : 2-*diphenylpyrazolidines. The* 4-*Hydroxy- and Certain* 4-*Alkoxy- and* 4-*Alkylamino-analogues.*

By (Mrs.) K. M. Hammond, N. Fisher, E. N. Morgan and (Miss) E. M. Tanner, with (in part) C. S. Franklin.

Dimethyl tetrahydropyranyloxymalonate reacts with hydrazobenzene to give 3 : 5-dioxo-1 : 2-diphenyl-4-tetrahydropyranyloxypyrazolidine. Removal of the tetrahydropyranyl group afforded 4-hydroxy-3 : 5-dioxo-1 : 2-diphenylpyrazolidine. A series of 4-alkoxy-3 : 5-dioxo-1 : 2-diphenylpyrazolidines has been prepared by interaction of alkoxymalonic esters with hydrazobenzene. 4-Alkoxy-3-hydroxy-1 : 2-diphenylpyrazolin-5-ones were isolated directly from condensations utilising diethyl methoxy- and ethoxymalonic esters; these are converted into the isomeric 4-alkoxy-3 : 5-dioxo-1 : 2-diphenylpyrazolidines. Condensations of *N*-benzyl-*N*-*n*-butyl- and *N*-benzyl-*N*-methyl-aminomalonates with hydrazobenzene and debenzylation of the resultant products gave the corresponding 4-*n*-butylamino- and 4-methylamino-3 : 5-dioxo-1 : 2-diphenylpyrazolidines.

Recent investigations into the anti-inflammatory activities of the 4-acyl-,[1] 4-alkyl-,[2,3] and 4-aminoalkyl-3 : 5-dioxo-1 : 2-diphenylpyrazolidines [1] have emphasised the high degree of specificity associated with the phenylbutazone structure (I; R = Bu^n). Syntheses are described, below, of the hitherto unknown 4-hydroxy-analogue (I; R = OH) and certain 4-alkoxy- (I; R = OMe, OEt, OPr^n, and OBu^n) and 4-alkylamino-3 : 5-dioxo-1 : 2-diphenylpyrazolidines (III; R = R′ = H, R″ = Me and Bu^n; R = H, R′ = R″ = Me).


(I)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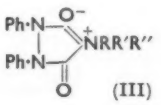
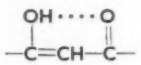
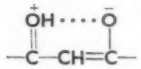

(III)

Condensation of dimethyl tetrahydropyranyloxymalonate [4] with hydrazobenzene in presence of sodium ethoxide [5] at 160—170° gave 3 : 5-dioxo-1 : 2-diphenyl-4-tetrahydropyranyloxypyrazolidine. This was converted by toluene-*p*-sulphonic acid in ethanol at room temperature into 4-hydroxy-3 : 5-dioxo-1 : 2-diphenylpyrazolidine (I; R = OH). An earlier attempt at the synthesis of the 4-hydroxy-analogue, utilising diethyl benzyloxymalonate in the initial condensation, failed owing to decomposition of the latter.

Under comparable conditions, diethyl methoxymalonate condensed with hydrazobenzene to give 3-hydroxy-4-methoxy-1 : 2-diphenyl-3-pyrazolin-5-one (II; R = OMe, R′ = H). This 4-methoxy- and the corresponding 4-ethoxy-pyrazolinone (II; R = OEt, R′ = H), similarly prepared, were comparatively unstable, and only the latter could be

(IV)   (V)

readily purified by recrystallisation. Their infrared spectra (Table) bore strong resemblances to those of the enolisable β-diketones, in having low OH frequencies (2700—2300 $cm.^{-1}$) and carbonyl frequencies as low as 1596 $cm.^{-1}$. Resonance between the forms (IV) and (V) is believed to be the reason for these anomalous frequencies in the enolisable

[1] Logemann, Lauria, and Zamboni, *Chem. Ber.*, 1955, **88**, 1353.
[2] Bavin, Drain, Seymour, and Waterhouse, *J. Pharm. Pharmacol.*, 1955, **7**, 1022.
[3] Budziarek, Drain, McCrae, McLean, Newbold, Seymour, Spring, and Stansfield, *J.*, 1955, 3158.
[4] Davoll and Laney, *J.*, 1956, 2124.
[5] Ruhkopf, *Ber.*, 1940, **73**, 820.

β-diketones,[6] and a similar effect is presumably operative in these 4-alkoxy-3-hydroxy-1 : 2-diphenyl-3-pyrazolin-5-ones. Characterisation of the acidic 4-methoxy- and 4-ethoxy-pyrazoline was achieved by conversion into the corresponding enol ethers (II; R = OMe, R′ = Me; R = OEt, R′ = Me) with ethereal diazomethane. In the double-bond region of their infrared spectra the strongest band, which is probably due to the amide-carbonyl group, is near 1635 cm.$^{-1}$, and the weaker, near 1690 cm.$^{-1}$, is due to the C=C double bond, although the latter is surprisingly high. This effect is not due to crystal structure as it persists in chloroform solution. Phenylbutazone reacts with ethereal diazomethane in a comparable manner, to give an enol ether (II; R = Bu^n, R′ = Me) with very similar infrared spectral characteristics.

Conversion of the enolic 4-methoxy- and 4-ethoxy-pyrazolines into the corresponding 4-alkoxy-3 : 5-dioxopyrazolidines (I; R = OMe and OEt) was achieved by recrystallisation from acetic acid.

In contrast, condensation of diethyl *n*-propoxy- and *n*-butoxy-malonate with hydrazobenzene furnished 3 : 5-dioxo-1 : 2-diphenyl-4-*n*-propoxy- (I; R = OPr^n) and 4-*n*-butoxy-3 : 5-dioxo-1 : 2-diphenylpyrazolidine (I; R = OBu^n) directly. The corresponding enolic pyrazolines were not encountered.

The neutral 4-alkoxy-3 : 5-dioxo-1 : 2-diphenylpyrazolidines do not react with ethereal diazomethane, and are not titratable, and their infrared spectra (Table) show carbonyl frequencies within the narrow range 1741—1747 cm.$^{-1}$ with a weaker component between 1754 and 1761 cm.$^{-1}$. Confirmation of their structure is found in the spectrum of the 4-*n*-butyl-4-methyl analogue where the tautomeric shift is blocked. The infrared spectrum of 4-hydroxy-3 : 5-dioxo-1 : 2-diphenylpyrazolidine closely resembles those of the 4-alkoxy-analogues although this compound exhibits anomalous behaviour on potentiometric titration and on treatment with ethereal diazomethane. The infrared spectrum of phenylbutazone [1] is similar to those of the 4-alkoxy-pyrazolidines although the C=O frequency is somewhat lower than in the latter.

Infrared spectra (*Nujol mulls*) (*cm.*$^{-1}$).

R	R′	R″	OH–NH region		Double-bond region					
4-Alkoxy-derivs., (a) *Pyrazolidines* (I)										
OH			3380		1763s	1713s		1598		1493
OMe					1761sh	1747s		1598		1490
OEt					1754sh	1747s		1595		1487
OPr^n					1754sh	1742s		1591		1484
OBu^n					1757sh	1741s		1591		1484
4-*n*-Butyl-4-methyl-					1754	1731s		1592		1481
(b) *Pyrazolines* (II)										
OMe	H		2715	2355	1742w	1710w	1641	1596s		1485
OEt	H		2730	2365	1751w	1715w	1636sh	1596s		1484
OMe	Me					1696	1635s	1591		1490
OEt	Me					1686	1636s	1591		1484
Bu^n	Me					1687	1640s	1594		1493
4-Amino-derivs. (III)										
H	H	H	2605w	2355w, 2045w		1710w	1675sh	1602s	1556, 1526sh	1493sh
H	H	Ac	3320		1772	1721s	1676s	1598	1496sh	1484sh
H	H	Me	2480	2370w	1946w		1696w	1604s	1583s	1496sh
H	H	Bu^n	2550, 2480	2370w			1691w	1601sh	1565s	1484
H	Me	Me	2690	2130w	1925w		1691w	1615s	1594sh	1482sh
Me	Me	Me					1682w	1615s	1598sh	1482sh

s = strong band; sh = shoulder; w = very weak band.

Ultraviolet absorption spectra of the 4-alkoxypyrazolidines in alcohol have their absorption maxima between 236 and 242 mμ, with only slight shifts with changes of pH; 4-ethoxy-3-hydroxy-1 : 2-diphenylpyrazolin-5-one shows a shift of maxima towards the longer wavelengths in 0·1N-sodium hydroxide, as would be expected.

[6] Rasmussen, Tunnicliff, and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1068.

The introduction of certain basic substituents into the 4-position of the 3 : 5-dioxo-1 : 2-diphenylpyrazolidine nucleus gave compounds possessing very different properties. A study of their behaviour on potentiometric titration revealed that the 4-amino-, 4-dimethylamino-, and 4-methylamino-3 : 5-dioxo-1 : 2-diphenylpyrazolidines had pK_a' values of 2·5 and 7·20; 2·5 and 8·57; and 2·5 and 8·17, respectively. These values closely resemble those of glycine (2·4 and 9·8). Additionally, the 4-dimethylamino-analogue reacted with ethereal diazomethane to give a neutral betaine;[7] and absence of strong infrared bands in the range 1741—1747 cm.$^{-1}$ and presence of other bands in the double-bond region comparable with those shown by the pyrazolines suggest that these compounds are best represented by the zwitterionic formula (III).

3 : 5-Dioxo-1 : 2-diphenylpyrazolidine (I; R = H), coupled with benzenediazonium chloride, furnished the 4-phenylazo-derivative (I; R = N:NPh). This could be reduced (i) catalytically with palladium–charcoal to the known 4-amino-compound[8] (III; R = R′ = R″ = H) or (ii) with zinc in acetic acid–acetic anhydride to the 4-acetamido-derivative (III; R = R′ = H, R″ = Ac). Condensation of diethyl dimethylaminomalonate with hydrazobenzene gave 4-dimethylamino-3 : 5-dioxo-1 : 2-diphenylpyrazolidine (III; R = H, R′ = R″ = Me) and this with ethereal diazomethane afforded a neutral betaine (III; R = R′ = R″ = Me). In a comparable manner, diethyl *N*-benzyl-*N*-methylamino- and diethyl *N*-benzyl-*N*-*n*-butylamino-malonate with hydrazobenzene gave 4-*N*-benzyl-*N*-methylamino- (III; R = H, R′ = CH_2Ph, R = Me) and 4-*N*-benzyl-*N*-*n*-butylamino-3 : 5-dioxo-1 : 2-diphenylpyrazolidine (III; R = H, R′ = CH_2Ph, R″ = Bu^n), respectively. Debenzylation of these compounds allowed the isolation of 4-methylamino- (III; R = R′ = H, R″ = Me) and 4-*n*-butylamino-3 : 5-dioxo-1 : 2-diphenylpyrazolidine (III; R = R′ = H, R″ = Bu^n) as pale orange, partially crystalline solids which were generally unstable, especially towards recrystallisation in bulk. Their ultraviolet spectra in alcohol were somewhat difficult to plot; results quoted were obtained by rapid measurement on freshly prepared solutions.

The compounds described in this paper were tested for anti-inflammatory activity by Dr. C. V. Winder of the Research Department, Parke, Davis & Co., Detroit. The tests did not reveal significant activity.

Experimental

Alkoxymalonic Esters.—Diethyl methoxymalonate was prepared from ethyl methoxyacetate, ethyl carbonate, and sodium ethoxide.[9] Similarly prepared were diethyl ethoxymalonate, *diethyl* n-*propoxymalonate*, b. p. 72—74°/0·2 mm., n_D^{20} 1·4228 (Found: C, 54·7; H, 8·2. $C_{10}H_{18}O_5$ requires C, 55·0; H, 8·3%), and *diethyl* n-*butoxymalonate*, b. p. 119—120°/3 mm., n_D^{20} 1·4253 (Found: C, 56·8; H, 8·5. $C_{11}H_{20}O_5$ requires C, 56·9; H, 8·7%).

Ethyl Benzyloxyacetate.—Benzyl alcohol (250 c.c.), potassium hydroxide (84 g.), and xylene (150 c.c.) were refluxed together with stirring until azeotropic removal of water was complete. To the resultant solution, ethyl chloroacetate (30 c.c.) was added at 120° (oil-bath) and the mixture refluxed until neutral. At the same temperature, 10N-sodium hydroxide (110 c.c.) was carefully added with stirring and reflux maintained for a further 1 hr. Then the mixture after dilution with water was steam-distilled, cooled, and extracted with ether. Subsequently, the aqueous phase was acidified and extracted with carbon tetrachloride. Evaporation of the solvent layer and distillation of the residue gave benzyloxyacetic acid (95 g.), b. p. 149—51°/1·5 mm., n_D^{23} 1·5280. Esterification furnished ethyl benzyloxyacetate (92%), b. p. 100—102°/1 mm., n_D^{22} 1·4970.

Diethyl Benzyloxymalonate.—Diethyl oxalate (73 g.) was added to a stirred suspension of sodium hydride (12 g.) in ether[10] (50 c.c.). To this, ethyl benzyloxyacetate (48·6 g.) was slowly (4 hr.) run in and the mixture refluxed for 1 hr. After cooling, the latter was poured into ice-water, acidified with acetic acid and extracted with ethyl acetate. Evaporation of the

[7] Kuhn and Brydowna, *Ber.*, 1937, **70**, 1333.
[8] Musante and Fabbrini, *Gazzetta*, 1954, **84**, 595.
[9] Ames and Bowman, *J.*, 1951, 1079.
[10] Soloway and La Forge, *J. Amer. Chem. Soc.*, 1947, **69**, 2677.

washed and dried solvent layer left an oil which was heated at 180—190° (oil-bath) under a vacuum for 8 hr. Final distillation gave *diethyl benzyloxymalonate* (18·6 g.), b. p. 134—138°/0·4 mm., n_D^{21} 1·4915 (Found: C, 63·0; H, 6·8. $C_{14}H_{18}O_5$ requires C, 63·1; H, 6·8%). The *diamide*, m. p. 226° (decomp.), crystallised from ethanol in needles (Found: C, 57·2; H, 5·9; N, 12·9. $C_{10}H_{12}O_3N_2$ requires C, 57·7; H, 5·8; N, 13·5%).

Aminomalonic Esters.—Diethyl *N*-benzyl-*N*-methylaminomalonate was prepared by the reaction of diethyl bromomalonate with *N*-benzylmethylamine in ethanol.[11] *Diethyl* N-*benzyl*-N-n-*butylaminomalonate*, b. p. 149—50°/0·3 mm., n_D^{20} 1·4845 (Found: C, 67·2; H, 8·4; N, 4·2. $C_{18}H_{27}O_4N$ requires C, 67·3; H, 8·5; N, 4·4%), was prepared in an analogous manner.

4-*Hydroxy*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine* (I; R = OH).—To a solution of sodium (0·04 g.-atom) in absolute ethanol (150 c.c.) was added dimethyl tetrahydropyranyloxymalonate (0·04 mole) and hydrazobenzene (0·04 mole). The ethanol was removed by distillation and the residue heated at 160—170° (oil-bath) under a vacuum for 2 hr. The crude product was extracted with ether and water, and the separated aqueous layer chilled and acidified with acetic acid (0·05 mol.). The white flocculent precipitate of 3 : 5-*dioxo*-1 : 2-*diphenyl*-4-*tetrahydropyranyloxypyrazolidine* (46%) which separated was filtered off and dried. It melted at ~60° but could not be recrystallised (Found: C, 67·7; H, 5·8; N, 8·0. $C_{20}H_{20}O_4N_2$ requires C, 68·2; H, 5·7; N, 8·0%).

The product (8·5 g.) was dissolved in warm absolute ethanol (250 c.c.), cooled, and treated with toluene-*p*-sulphonic acid (0·15 g.). Overnight there separated rectangular prisms of 4-*hydroxy*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine ethanol solvate* (3·75 g.), m. p. 201—203° (decomp.) (Found: C, 65·2; H, 5·7; N, 9·3. $C_{15}H_{12}O_3N_2,C_2H_5{\cdot}OH$ requires C, 65·0; H, 5·8; N, 8·9%). Recrystallisation of this from 2-methoxyethanol and drying at 100°/1 hr. in a high vacuum gave the parent 4-*hydroxy-compound*, m. p. 211—213° (decomp.) (Found: C, 67·1; H, 4·8; N, 10·0. $C_{15}H_{12}O_3N_2$ requires C, 67·2; H, 4·5; N, 10·4%). Ultraviolet absorption in EtOH: $\lambda_{max.}$ 235 mμ (ε 18,500).

4-*Methoxy*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine* (I; R = OMe).—Likewise, the crude product obtained from a condensation between diethyl methoxymalonate and hydrazobenzene was extracted with ether and water. Acidification of the aqueous layer gave a precipitate which when dried and recrystallised from aqueous ethanol gave microscopic flattened needles of 3-*hydroxy*-4-*methoxy*-1 : 2-*diphenylpyrazolin*-5-*one* (II; R = OMe, R′ = H), m. p. 130—131° (58%) (Found: C, 68·5; H, 5·2; N, 9·9. $C_{16}H_{14}O_3N_2$ requires C, 68·1; H, 5·0; N, 9·9%). The latter with ethereal diazomethane gave the 3-*methyl ether* (II; R = OMe, R′ = Me), m. p. 173—174° (Found: C, 69·1; H, 5·4; N, 9·7. $C_{17}H_{16}O_3N_2$ requires C, 68·9; H, 5·4; N, 9·5%), which separated in needles from aqueous ethanol. Ultraviolet absorption in EtOH: $\lambda_{max.}$ 257 mμ (ε 17,900). Recrystallisation of the 3-hydroxy-compound from aqueous acetic acid and finally from 2-methoxyethanol furnished colourless hexagonal tablets of 4-*methoxy*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine*, m. p. 248—250° (decomp.) (Found: C, 68·4; H, 5·0; N, 10·0. $C_{16}H_{14}O_3N_2$ requires C, 68·1; H, 5·0; N, 9·9%). Ultraviolet absorption in EtOH: $\lambda_{max.}$ 236 mμ (ε 13,600). This compound does not react with ethereal diazomethane.

Similarly prepared, 4-*ethoxy*-3-*hydroxy*-1 : 2-*diphenylpyrazolin*-5-*one* (II; R = OEt, R′ = H), m. p. 148—150° (40%) (Found: C, 69·2; H, 5·5; N, 9·6. $C_{17}H_{16}O_3N_2$ requires C, 68·9; H, 5·4; N, 9·5%), recrystallised from aqueous ethanol in colourless flattened needles. The pK_a' in 50% aqueous EtOH was 3·55. Ultraviolet absorption max.: in EtOH, 237, 240, 273 (sh) mμ (ε 14,500, 14,500, and 8170); in 0·1N-sodium hydroxide, 265 mμ (ε 15,100). The derived 3-*methyl ether* (II; R = OEt, R′ = Me), m. p. 98—99° (Found: C, 69·7; H, 5·9; N, 9·0. $C_{18}H_{18}O_3N_2$ requires C, 69·7; H, 5·9; N, 9·0%), separated in colourless needles from aqueous methanol. Ultraviolet absorption in EtOH: $\lambda_{max.}$ 259 mμ (ε 17,300). Further recrystallisation of 4-ethoxy-3-hydroxy-1 : 2-diphenylpyrazolin-5-one from acetic acid converted it into 4-*ethoxy*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine* (I; R = OEt) which separated in stout needles, m. p. 240—242° (decomp.), from ethyl methyl ketone (Found: C, 68·9; H, 5·4; N, 9·6. $C_{17}H_{16}O_3N_2$ requires C, 68·9; H, 5·4; N, 9·5%). Ultraviolet absorption in EtOH: $\lambda_{max.}$ 238, 241 mμ (ε 13,600, 13,500).

3 : 5-*Dioxo*-1 : 2-*diphenyl*-4-n-*propoxypyrazolidine* (I; R = OPr^n), m. p. 228—229° (decomp.) (Found: C, 69·7; H, 5·7; N, 8·8. $C_{18}H_{18}O_3N_2$ requires C, 69·7; H, 5·9; N, 9·0%), flattened needles from 2-methoxyethanol, and 4-n-*butoxy*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine* (I; R = OBu^n), m. p. 242—244° (decomp.) (Found: C, 70·7; H, 6·0; N, 8·7. $C_{19}H_{20}O_3N_2$ requires C,

[11] Hardegger and Corrodi, *Helv. Chim. Acta*, 1956, **39**, 980.

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70·4; H, 6·2; N, 8·6%), flattened needles from ethyl methyl ketone, were prepared in an analogous manner. Ultraviolet absorptions in EtOH: $\lambda_{max.}$ 242 mμ (ε 14,300) and 242 mμ (ε 14,400) respectively. In the preparations of the 4-*n*-propoxy- and the 4-*n*-butoxy-analogue the enolic pyrazolines were not encountered.

4-n-*Butyl*-3-*methoxy*-1 : 2-*diphenyl*-3-*pyrazolin*-5-*one* (II; R′ = Me, R = Bu^n).—Treatment of phenylbutazone with ethereal diazomethane afforded, in the usual manner, the 3-*methyl ether*, m. p. 91—92° (Found: C, 74·3; H, 6·9; N, 8·8. $C_{20}H_{22}O_2N_2$ requires C, 74·5; H, 6·9; N, 8·7%), which crystallised from light petroleum (b. p. 80—100°) in colourless plates. Ultraviolet absorption in EtOH: $\lambda_{max.}$ 253 mμ (ε 15,800).

3 : 5-*Dioxo*-1 : 2-*diphenyl*-4-*phenylazopyrazolidine* (I; R = N:NPh).—To a stirred suspension of 3 : 5-dioxo-1 : 2-diphenylpyrazolidine (0·1 mole) in water (500 c.c.), containing sodium acetate (0·5 mole) at 5° were added chloroform (250 c.c.) and an aqueous solution of benzenediazonium chloride (0·1 mole). After 2 hr., the separated chloroform layer was combined with a chloroform washing of the aqueous layer and evaporated to dryness. Crystallisation of the residue from ethanol gave orange needles of 3 : 5-*dioxo*-1 : 2-*diphenyl*-4-*phenylazopyrazolidine*, m. p. 184—186° (94%) (Found: C, 71·0; H, 4·5. $C_{21}H_{16}O_2N_4$ requires C, 70·8; H, 4·5%).

4-*Amino*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine* (III; R = R′ = R″ = H).—The foregoing azo-compound (3·5 g.) in absolute alcohol (60 c.c.) was shaken with 15% palladium–charcoal (1 g.) under normal conditions until uptake of hydrogen was complete. After addition of N-sodium hydroxide (10 c.c.), the mixture was again shaken for a few minutes, then the catalyst was filtered off. Addition of N-hydrochloric acid (10 c.c.) to the filtrate precipitated partially crystalline (needles), buff-coloured 4-amino-3 : 5-dioxo-1 : 2-diphenylpyrazolidine, m. p. 229—230° (decomp.) (1·8 g.) (Found: C, 67·3; H, 5·4. Calc. for $C_{15}H_{13}O_2N_3$: C, 67·4; H, 4·9%). The values for pK_{a_1}' and pK_{a_2}' in 50% EtOH were 2·5 and 7·20 respectively. Ultraviolet absorption in EtOH: $\lambda_{max.}$ 244, 252 (sh) mμ (ε 13,200, 12,600). This compound, for which Musante and Fabbrini [8] recorded m. p. 197—200° (decomp.), separated in yellowish needles from aqueous alcohol, when recrystallised in small amounts. The iso*propylidene derivative*, m. p. 201° (decomp.) (Found: C, 70·3; H, 5·8; N, 13·7. $C_{18}H_{17}O_2N_3$ requires C, 70·3; H, 5·6; N, 13·7%), prepared by refluxing the foregoing compound in acetone, separated in colourless needles from methanol. The *acetyl derivative*, m. p. 190° (Found: C, 65·3; H, 5·1. $C_{17}H_{15}O_3N_3$ requires C, 66·0; H, 4·9%), which crystallised from benzene in colourless prisms, was obtained by (i) direct acetylation (acetic anhydride) of the 4-amino-compound and (ii) by reduction of the 4-phenylazo-compound. A solution of the latter (1·8 g.) in acetic acid (25 c.c.) containing acetic anhydride (10 c.c.) was treated with zinc dust (6 g.), at <40°. After 1 hr. at room temperature, the mixture was filtered and the filtrate evaporated. Recrystallisation of the residue from benzene furnished the 4-acetamido-derivative, the mixed m. p. with the compound prepared by direct acetylation being undepressed.

4-*Dimethylamino*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine* (III; R = H, R′ = R″ = Me).—Diethyl dimethylaminomalonate [12] (10·2 g.) in xylene (100 c.c.) was refluxed with sodium hydride (1·2 g.) for 0·5 hr. To the resultant suspension of diethyl sodiodimethylaminomalonate, hydrazobenzene (9·2 g.) in xylene (50 c.c.) was added and the mixture refluxed 2 hr. On cooling, the mixture was extracted with water and the combined aqueous extracts were acidified with dilute hydrochloric acid. Recrystallisation of the dried precipitate from aqueous acetic acid furnished colourless plates of 4-*dimethylamino*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine*, m. p. 196—197° (decomp.) (Found: C, 69·2; H, 5·7. $C_{17}H_{17}O_2N_3$ requires C, 69·1; H, 5·8%). The values for pK_{a_1}' and pK_{a_2}' in 50% EtOH were 2·5 and 8·57. Ultraviolet absorption in EtOH: $\lambda_{max.}$ 253 mμ (ε 21,970).

Similarly prepared from the requisite malonic esters were 4-N-*benzyl*-N-*methylamino*- m. p. 179—180° (decomp.) (Found: C, 74·7; H, 5·8; N, 11·3. $C_{23}H_{21}O_2N_3$ requires C, 74·4; H, 5·7; N, 11·3%), tablets from ethyl methyl ketone, and 4-N-*benzyl*-N-n-*butylamino*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine*, m. p. 184—185° (decomp.) (Found: 71·0; H, 6·2; N, 9·0. $C_{26}H_{27}O_2N_3,CH_3{\cdot}CO_2H$ requires C, 71·0; H, 6·6; N, 8·0%), tablets from aqueous acetic acid.

4-*Methylamino*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine* (III; R = R′ = H, R″ = Me).—The foregoing *N*-benzyl-*N*-methylamino-compound (5·6 g.), suspended in ethanol (100 c.c.), was shaken with 10% palladium–charcoal (2 g.) in hydrogen. The original solid slowly dissolved and when the uptake of hydrogen was complete the resulting fine white precipitate was redissolved by adding N-sodium hydroxide (15 c.c.), and the mixture filtered. Acidification of

[12] Jones and Wilson, *J.*, 1949, 550.

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the filtrate with N-hydrochloric acid (15 c.c.) precipitated **4-*methylamino*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine***, m. p. 171—173° (decomp.), as a partially crystalline orange solid (2·7 g.) (Found : C, 68·6; H, 5·6; N, 14·4. $C_{16}H_{15}O_2N_3$ requires C, 68·3; H, 5·3; N, 14·9%). The pK_{a_1}' and pK_{a_2}' values in 50% EtOH were 2·5 and 8·17. Ultraviolet absorption in EtOH : $\lambda_{max.}$ 236, 238, 245 (sh) mμ (ε 15,000, 15,000, 14,300).

4-n-*Butylamino*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine* (III; R = R′ = H, R″ = Bu^n), m. p. 190—191° (decomp.) (Found : C, 70·0; H, 6·6; N, 12·5. $C_{19}H_{21}O_2N_3$ requires C, 70·6; H, 6·6; N, 13·0%), was obtained in a comparable manner, as an orange, partially crystalline powder. Owing to instability and poor solubility potentiometric titrations were not completed. Ultraviolet absorption in EtOH : $\lambda_{max.}$ 237, 240 mμ (ε 16,500, 16,400).

5-Hydroxy*-1 : 2-*diphenyl*-4-*trimethylammoniopyrazol*-3-*one betaine (III; R = R′ = R″ = Me).—4-Dimethylamino-3 : 5-dioxo-1 : 2-diphenylpyrazolidine (5 g.), finely powdered and suspended in ether containing a little methanol, was treated with ethereal diazomethane, and the mixture kept overnight at room temperature. The insoluble material (1·6 g.) was filtered off and recrystallised from 2-methoxyethanol, to give hexagonal plates of the ***betaine***, m. p. 267—268° (decomp.) (Found : C, 69·8; H, 6·0; N, 13·6. $C_{18}H_{19}O_2N_3$ requires C, 69·9; H, 6·2; N, 13·6%). This compound is not titratable between pH 2·5 and 11.

Infrared spectra were recorded with a Grubb Parsons DBI/S3A spectrometer, and ultraviolet absorption measurements were made on a Unicam S.P.500 spectrophotometer.

The authors thank Mr. D. E. Seymour, of Smith & Nephew Research Ltd., for the sample of 4-*n*-butyl-4-methyl-1 : 2-diphenylpyrazolidine, and Dr. R. E. Bowman for many helpful discussions. Microanalyses are by Mr. A. J. Durre.

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209. *Synthesis of Adenosine-5′ Sulphatophosphate. A Degradation Product of an Intermediate in the Enzymic Synthesis of Sulphuric Esters.*

By J. BADDILEY, J. G. BUCHANAN, and R. LETTERS.

Adenosine-5′ sulphatophosphate (Ib) has been synthesised from adenosine-5′ phosphate and the pyridine–sulphur trioxide complex in sodium hydrogen carbonate solution. It was identical with a substance obtained by enzymic dephosphorylation of adenosine 3′-phosphate 5′-sulphatophosphate (Ia) (an intermediate formed from adenosine triphosphate and inorganic sulphate during the enzymic synthesis of sulphuric esters).

The sulphatophosphate linkage in (Ib) is hydrolysed by an enzyme in rattlesnake venom.

SULPHURIC ESTERS are frequently found in Nature as structural materials (*e.g.*, sulphuric esters of carbohydrates), and as excretory products ("ethereal sulphates"). It is believed that phenols and other hydroxy-compounds are converted into their sulphuric esters in the liver by enzymic processes which utilise inorganic sulphate. Adenosine triphosphate (ATP) is required in these reactions [1,2] which involve several stages.[3] The overall process can be separated into an "activation" of sulphate, followed by a transfer of the sulphate group to the phenol.[4] An intermediate was formed when ATP and sulphate were incubated with enzyme preparations in the absence of phenols.

Lipmann and his associates [5] have examined these reactions and in particular the nature of "active sulphate." This intermediate was an adenine derivative bearing a

[1] Bernstein and McGilvery, *J. Biol. Chem.*, 1952, **198**, 195.
[2] DeMeio, Wizerkaniuk, and Fabiani, *ibid.*, 1953, **203**, 257.
[3] DeMeio, Wizerkaniuk, and Schreibman, *ibid.*, 1955, **213**, 439.
[4] Bernstein and McGilvery, *ibid.*, 1952, **199**, 745.
[5] Robbins and Lipmann, *J. Amer. Chem. Soc.*, 1956, **78**, 2652, and personal communication.

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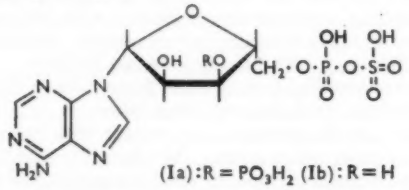
sulphate and two phosphate groups. The sulphate was readily removed by acid hydrolysis, a secondary phosphate being liberated. The nucleoside-3′ phosphatase from rye grass removed one phosphate group without loss of sulphate. This and other evidence indicated the structure adenosine 3′-phosphate 5′-sulphatophosphate (Ia) for the active sulphation intermediate. The product of its enzymic dephosphorylation would be adenosine-5′ sulphatophosphate (Ib).



(Ia): R = PO_3H_2 (Ib): R = H

Although it has been claimed [6] that salts of sulphatophosphoric acid are formed when sulphuric acid and alkali-metal phosphates are heated together under suitable conditions, their characterisation is inadequate. Further, esters of sulphatophosphoric acid have not been described previously and it was of interest to attempt the synthesis and chemical study of such compounds.

A total synthesis of adenosine 3′-phosphate 5′-sulphatophosphate (Ia) would present special difficulties in view of the unavailability of adenosine-3′ : 5′ diphosphate or its derivatives. The latter nucleotide is known as an enzymic degradation product of coenzyme A, but its preparation in quantity from this source would be difficult and costly. Consequently, the somewhat simpler synthesis of adenosine-5′ sulphatophosphate (Ib) was undertaken. This product should be identical with that obtained by enzymic dephosphorylation of the 3′-phosphate (Ia), thereby confirming the structure assigned to the latter. The synthetic compound would also be of interest in enzyme studies.

There has been much progress recently on the synthesis of anhydrides of phosphoric acid, mainly confined, however, to the formation of symmetrical and unsymmetrical esters of pyro- and tri-phosphoric acid. Relatively little attention has been given to the synthesis of mixed anhydrides between a nucleotide and another acid. The use of carbodi-imides in the preparation of mixed anhydrides of this type was considered, since these reagents can be used for the synthesis of both pyrophosphates [7] and sulphonic anhydrides [8] from the parent acids. Condensation was attempted between phosphoric and sulphuric acid in the presence of di*cyclo*hexylcarbodi-imide under a variety of conditions. In most cases the reaction products, when examined by paper electrophoresis, were complex, but no good evidence for the formation of mixed anhydrides was obtained.

A general synthesis of mixed anhydrides of carboxylic acids with phosphoric acid and its esters, developed by Avison,[9] involves reaction between phosphates and appropriate anhydrides of carboxylic acids in aqueous pyridine at a low temperature, in which anhydride–pyridine complexes probably participate. The compound obtained by the action of sulphur trioxide on pyridine [10] (" pyridine-*N*-sulphonic acid ") was considered suitable as the anhydride component for the preparation of sulphatophosphates. It was added to a cold aqueous-pyridine solution of adenosine-5′ phosphate, and the mixture was examined by paper chromatography. Much unchanged nucleotide was present, and the only other product which absorbed ultraviolet light on paper was a compound with a higher R_F in basic solvents. Considerably more of the faster-moving nucleotide was obtained by reaction at 40—50° in sodium hydrogen carbonate solution : it was estimated

[6] Cf. Mellor, " A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans Green and Co., 1930, Vol. X, p. 437.
[7] Khorana and Todd, *J.*, 1953, 2254.
[8] Khorana, *Canad. J. Chem.*, 1953, **31**, 585.
[9] Avison, *J.*, 1955, 732.
[10] Baumgarten, *Ber.*, 1926, **59**, 1166.

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by ultraviolet spectroscopy that approximately 20% of the total nucleotides was then present as the faster-moving compound. The product was isolated in small amounts by adsorption on charcoal, elution with dilute ammonia, and paper chromatography in two solvent systems. It moved as a single spot on paper and on electrophoresis, and did not contain inorganic sulphate. It had an ultraviolet spectrum typical of an adenosine derivative with no additional substituents on the ring-nitrogen atoms or on the 6-amino-group. It was fairly stable in cold neutral or dilute alkaline solution, but was hydrolysed readily in hot dilute acid and alkali to inorganic sulphate and adenosine-5′ phosphate. These products were identified on paper, the inorganic sulphate being detected by spraying the paper with very dilute barium chloride solution, followed by a solution of rhodizonic acid; sulphate appeared as a white spot against a pink background. The nucleotide was completely hydrolysed in 0·5N-hydrochloric acid at 100° after 15 min. The ratio adenine : sulphate was 1 : 0·95, as determined from the light absorption of its solution at 260 mμ and the amount of sulphate (as barium sulphate) liberated on acid hydrolysis. No substituents were present at position 2′ or 3′, since it gave a strong colour reaction on paper when sprayed with periodate followed by Schiff's reagent. It was concluded that the substance was a sulphatophosphate with the structure (Ib).

Adenosine-5′ sulphatophosphate was isolated as its lithium salt after gradient-elution chromatography on Dowex-2 resin (formate form), elution being effected with ammonium formate solution. The lithium salt was analytically pure, although it contained a trace of adenosine-5′ phosphate, and had an absorption spectrum similar to those of the adenosine phosphates. It consumed one mol. of periodate, thus confirming the absence of substituents at positions 2′ and 3′.

The synthetic material was indistinguishable from the product of enzymic dephosphorylation of the natural compound (Ia) on paper chromatography and on electrophoresis. At pH 5 it migrated towards the anode at a rate very slightly greater than that of adenosine-5′ pyrophosphate, whereas at pH 8 it had a rate similar to that of adenosine-5′ phosphate. These results are consistent with the presence of two primary acidic dissociations in the molecule.

Enzymes present in rattlesnake (*Crotalus atrox*) venom hydrolysed adenosine-5′ sulphatophosphate to adenosine, orthophosphate, and sulphate. The unfractionated venom is known to contain nucleoside-5′ phosphatase, pyrophosphatase, and phosphodiesterase. It is not yet known whether it also contains a specific sulphatophosphatase or whether pyrophosphatases are responsible for the hydrolysis.

Experimental

Adenosine-5′ Sulphatophosphate.—The pyridine–sulphur trioxide complex (400 mg.; m. p. 172°) was added with stirring to a solution of adenosine-5′ phosphate (200 mg.) and sodium hydrogen carbonate (350 mg.) in water (5 c.c.) at 40—50°. After 15 min. at this temperature, stirring was discontinued and the solution was cooled in iced water. A sample of the mixture was examined by paper chromatography in solvent systems A and B (see below). Adenosine-5′ phosphate and the sulphatophosphate were the principal components absorbing ultraviolet light. Only traces of other nucleotides were detected. Spots were eluted from the paper and the optical density of the resulting solution was measured at 260 mμ. On the assumption that the sulphatophosphate has an extinction coefficient at 260 mμ typical of an adenosine-5′ phosphate derivative, about 20% of the starting material had been converted into the sulphatophosphate.

The above mixture was diluted to 250 c.c., adjusted to pH 5·5 with 2M-formic acid, and shaken overnight with Norit A charcoal (10 g.) which had previously been washed with 2M-formic acid (200 c.c.), ethanolic ammonia [water, 100 c.c.; alcohol, 96 c.c.; ammonia (*d* 0·88), 4 c.c.], and finally water (600 c.c.). The charcoal containing the nucleotides was filtered off and washed with water (400 c.c.). The nucleotide content of the filtrate and washings was less than 0·5 mg., as determined by optical density at 260 mμ. Nearly all the inorganic sulphate formed during the reaction was present in this filtrate and washings. Nucleotides were eluted

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from the charcoal with ethanolic ammonia (200 c.c.; composition as above). The optical density at 260 mμ of the eluate indicated a recovery of 95%. Without delay, the eluate was concentrated (to 4 c.c.) *in vacuo*, and the sulphatophosphate was separated from adenosine-5′ phosphate and traces of inorganic sulphate by chromatography as a series of spots on Whatman No. 3 paper in the solvent system B. The sulphatophosphate was homogeneous when examined by paper chromatography in solvent systems A and B (yield 18·1%, based on optical density).

A solution of the purified sulphatophosphate was divided into two equal parts. The " adenine " content (3·17 mg.) of one part was determined by optical density at 260 mμ, and the other part was treated with 0·5N-hydrochloric acid at 100° for 30 min. Inorganic sulphate was determined in this part by precipitation as barium sulphate (ratio of adenine : sulphate, 1 : 0·95. Adenosine-5′ sulphatophosphate requires ratio, 1 : 1).

Isolation. The sulphatophosphate (from 200 mg. of adenosine-5′ phosphate and 200 mg. of sulphur trioxide complex) was prepared as above, the reaction being carried out during 30 min. The solution was diluted with water (1 l.) and passed through a column (10 × 3 cm.) of Dowex-2 (formate) resin which was then washed with distilled water (300 c.c.). Elution was carried out with ammonium formate solution (pH 5) in an apparatus designed to give an approximately linear concentration/volume gradient during the delivery of about 3 l. of eluant. The final concentration of ammonium formate was 2M. Elution of adenosine-5′ phosphate was complete after about 1200 c.c. of eluant had been collected. The sulphatophosphate was eluted in the range 2400—3000 c.c.

The fractions containing the sulphatophosphate were bulked and shaken with Norit A charcoal (3 g.) overnight. The charcoal was filtered off and washed with water (300 c.c.), and the nucleotide was eluted with 50% ethanol containing 2% of ammonia. The eluate was concentrated to about 10 c.c., then passed through a column (2 × 1 cm.) of Dowex-50 (lithium form) resin. The column was washed with water until free from material absorbing ultraviolet light, and the combined eluate and washings were freeze-dried. The resulting solid was dissolved in water (2 c.c.), and ethanol (20 c.c.) was added. The precipitated *lithium salt* (11·6 mg.) was collected by centrifugation (Found : P, 6·9. $C_{10}H_{14}O_{10}N_5SPLi_2$ requires P, 7·1%).

The lithium salt had $\lambda_{max.}$ 259 mμ (ε 15,200) and $\lambda_{min.}$ 227 mμ (ε 2620) at pH 7—8. This spectrum corresponded closely with that reported [11] for adenosine-5′ phosphate [$\lambda_{max.}$ 259 mμ (ε 15,400) and $\lambda_{min.}$ 227 mμ (ε 2600) at pH 7]. It consumed 0·98 mol. of periodate, determined spectrophotometrically.[12]

Unchanged adenosine-5′ phosphate was recovered from the above synthesis. The appropriate fractions from the ion-exchange column were bulked and shaken overnight with Norit A charcoal. Elution was carried out as described for the sulphatophosphate, and ammonium ions were removed from the concentrated eluate by passage through a Dowex-50 (H^+ form) resin column. Concentration of the eluate from this column yielded the crystalline phosphate (100 mg.).

Paper Chromatography.—Ascending-front chromatography was carried out on Whatman No. 4 paper, previously washed with dilute acetic acid and water. The following solvent systems were used : (A) *n*-propyl alcohol–ammonia (*d* 0·88)–water (6 : 3 : 1); (B) *iso*butyric acid–0·5N-ammonia (5 : 3). Nucleotides were located by inspection under ultraviolet light, by the perchloric acid–molybdate spray reagent for phosphate, and by the periodate–Schiff reagent for glycols. R_F values are shown in the Table. Synthetic and natural adenosine-5′ sulphatophosphate were indistinguishable in both solvents.

	R_F values in solvent			R_F values in solvent	
Adenosine-5′	A	B		A	B
Phosphate	0·40	0·50	Inorg. sulphate	—	0·20
Pyrophosphate	0·30	0·40	Inorg. phosphate	—	0·25
Sulphatophosphate	0·63	0·32			

Paper Electrophoresis.—Electrophoresis was carried out on Whatman No. 4 paper soaked in 0·05M-ammonium acetate buffers at pH 5·5 and 8·5. Drs. Robbins and Lipmann used a 0·025M-citrate buffer at pH 5·8. Our experiments (see Table) were for 3 hr. with a voltage gradient of 5·4 v per cm. and a current of 7·5 milliamps.

[11] Morell and Bock, 126th Meeting Amer. Chem Soc., New York, 1954, Div. of Biol. Chem., Abs., p. 44 c.
[12] Dixon and Lipkin, *Analyt. Chem.*, 1954, **26**, 1092.

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	Distance moved towards cathode (cm.)		
	pH 5·5	pH 8·5	pH 5·8 *
Adenosine-5′ phosphate	4·6	6·4	24·5
Adenosine-5′ pyrophosphate	9·5	10·5	34·0
Adenosine-5′ sulphatophosphate	9·7	8·8	34·5

* Experiments carried out by Drs. Robbins and Lipmann (voltage and time not stated).

Detection of Inorganic Sulphate on Paper Chromatograms.—Chromatograms run as described above were lightly sprayed with a solution of barium chloride (60 mg.) in water (250 c.c.), followed immediately by a solution of rhodizonic acid (5 mg.) in water (20 c.c.). Areas which contained inorganic sulphate appeared white on a pink background.

Action of Crotalus atrox *Venom on Adenosine-5′ Sulphatophosphate.*—A solution of the lithium salt (0·1 mg.) and venom (1 mg.) in a glycine–ammonia buffer (0·1 c.c.) at pH 9 was kept at 37° overnight. Samples were examined by paper chromatography in solvent system B. The products were identified by their R_F values (see Table) and by appropriate spray reagents as adenosine, orthophosphate, and sulphate. In a control experiment to which no enzyme had been added no spontaneous hydrolysis was observed.

We thank Drs. Robbins and Lipmann for a sample of enzymically prepared adenosine-5′ sulphatophosphate. One of us (R. L.) thanks the Council of King's College for the award of a Johnston Studentship.

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Newcastle upon Tyne. [*Received, November 7th*, 1956.]

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210. *The Analysis of Rotatory Dispersion: 2 : 3-Epoxypropyl Phenyl Ether.*

By M. K. Hargreaves.

The method of analysis of rotation–temperature curves in terms of an equilibrium mixture of isomeric forms or conformations is examined and the accuracy required for its use discussed. An attempt has been made to resolve the rotatory dispersion of 2 : 3-epoxypropyl phenyl ether into those of two forms by analysis of the specific rotation–temperature curves. Calculations show that the difference in the heat content of two such forms is of the order 2·5—3 kcal./mole.

Kauzmann, Walter, and Eyring [1] have calculated "rotatory constants" a and b for three esters of tartaric acid from the variation of the specific rotation with temperature. These "rotatory constants" represent the rotatory power, at a given wavelength, of two presumed forms or conformations, A and B, of the molecule, the proportions of each form present in the equilibrium mixture varying with the temperature. These forms may be chemically different isomers or merely "rotational" isomers. This method of analysis should have considerable application in the study of rotatory dispersion. An attempt has therefore been made to repeat the calculations which were based on experimental work by Winther.[2] Kauzmann, Walter, and Eyring do not give their method of solution and since there are discrepancies between their results and those now obtained a brief account of the method now used is given.

Form of Solution.—The expression for the equilibrium of two forms B $\rightleftharpoons$ A may be written

$$(b - \alpha)/(\alpha - a) = \exp(\Delta S/\boldsymbol{R} - \Delta H/\boldsymbol{RT}) \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where α, for simplicity, is the specific rotation.

[1] Kauzmann, Walter, and Eyring, *Chem. Reviews*, 1940, **26**, 339.
[2] Winther, *Z. phys. Chem.*, 1902, **41**, 161.

A solution to equation (1) can be obtained by using a pair of temperatures to eliminate ΔS, giving

$$\ln\left(\frac{b-\alpha_1}{\alpha_1-a}\cdot\frac{\alpha_2-a}{b-\alpha_2}\right)=-\frac{\Delta H}{R}\left(\frac{1}{T_1}-\frac{1}{T_2}\right) \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The right-hand side of this equation may be eliminated by choosing two temperatures T_3 and T_4, such that $(T_4-T_3)/T_4T_3=(T_2-T_1)/T_2T_1$. We then obtain

$$\frac{b-\alpha_1}{\alpha_1-a}\cdot\frac{\alpha_2-a}{b-\alpha_2}=\frac{b-\alpha_3}{\alpha_3-a}\cdot\frac{\alpha_4-a}{b-\alpha_4} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

This equation can be developed into the form

$$b=-\left(\frac{Z+pa}{p+qa}\right). \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where $p=(\alpha_2\alpha_3-\alpha_1\alpha_4)$, $q=(\alpha_1+\alpha_4-\alpha_2-\alpha_3)$,

and $Z=(\alpha_1\alpha_3\alpha_4+\alpha_1\alpha_2\alpha_4-\alpha_2\alpha_3\alpha_4-\alpha_1\alpha_2\alpha_3)$

The solution of this equation requires a further set of values p', q', and z', obtained from α'_1, α'_2, α'_3, and α'_4 (corresponding to temperatures T'_1, T'_2, T'_3, and T'_4), of which at least one value differs from the previous set. Thus, although there are only four unknowns at least five values are required for a solution:

$$a=\sqrt{\left[\frac{p'z-z'p}{p'q-q'p}+\frac{1}{4}\left(\frac{z'q-q'z}{p'q-q'p}\right)^2\right]}-\frac{1}{2}\left(\frac{z'q-q'z}{p'q-q'p}\right) \quad . \quad . \quad . \quad (5)$$

Substitution in equation (4) then gives b and in equation (2) ΔH; ΔS is obtained from equation (1).

The author is indebted to Dr. R. G. Taylor for an alternative method which involves differentiation of equation (1) to give $R(a-b)/\Delta H\,.\,d\alpha/dT\,.\,T^2=-\alpha^2+(a+b)\alpha-ab$. By reading $d\alpha/dT$ from a graph for three values of T, a solution is possible, though this requires an accuracy in the estimation of $d\alpha/dT$ which is not usually obtainable.

Attempts to calculate the difference in the heat content of the two forms, ΔH, the entropy difference, ΔS, and the rotatory constants, a and b, for dimethyl tartrate from the optical rotation–temperature curve for light of wavelength 5890 Å yield imaginary results. It is shown below that small variations in experimental values, or possibly, in this case, variations in method of calculation may produce very large variations in the results, though a and b are generally more affected than ΔH. The corresponding curve for $\lambda=5890$ Å appears to be accurate but its form results in terms in the solution being of almost vanishing magnitude. The other curves do not give such a good plot and in these cases also no solution was obtainable by our method. Kauzmann, Walter, and Eyring found for dimethyl tartrate:

for $\lambda=5890$ Å; $\Delta H=2280$ cal./mole, $\Delta S=10{\cdot}6$ e.u./mole, $a=10{\cdot}2$, $b=-30$
for $\lambda=4703$ Å; $\Delta H=2280$ cal./mole, $\Delta S=10{\cdot}6$ e.u./mole, $a=10{\cdot}9$, $b=-61$
for $\lambda=4445$ Å; $\Delta H=2280$ cal./mole, $\Delta S=10{\cdot}6$ e.u./mole, $a=11{\cdot}1$, $b=-81$

It would seem that the constants they calculated must all have been obtained from the 5890 Å curve so that the other curves do not provide an independent check. Another possibility is that the values of ΔH, etc., are arbitrary. The fit of the calculated to the observed values is, however, impressive. With diethyl tartrate a similar divergence of results is found, and if the previous results were derived directly from the experimental points it must be assumed that some method of selection was used which was not given.

Experimental Error and the Accuracy of the Solution of the "Two-form" Equation.— A precise arithmetical analysis of the solutions of these equations is required to determine

the circumstances in which those solutions are valid; such an analysis is outside the scope of the present work. It is emphasised that the solution given below is an exact algebraic solution; difficulties arise only when the experimental values are substituted in the equation. The final error appears not to be related in any simple way to the error of observation but depends on the position of the observed point on the specific rotation–temperature curve. The difficulties are almost exactly those encountered in the solution of two-term Drude equations where also the products of small numbers with the differences of their powers occur. The error in ΔH is likely to be less than that of the " constants " a and b from which it is derived. For example, one of the points in the specific rotation–temperature curve for $\lambda = 6438$ Å for 2 : 3-epoxypropyl phenyl ether (see below) is clearly seen to be in error when the experimental results are plotted on a large scale. The curve can be drawn so as to give, *e.g.*, $\alpha_4 = 11{\cdot}75$ and $\alpha'_3 = 12{\cdot}56$ or $\alpha_4 = 11{\cdot}77$ and $\alpha'_3 = 12{\cdot}58$, from which are calculated the values $a = 45{\cdot}2$, $b = 0{\cdot}63$, $\Delta H = 3194{\cdot}2$, and $a = 108$, $b = -6{\cdot}0$, $\Delta H = -1624$ cal./mole, respectively. On the other hand the reduction of α_1, α_2, α'_1 and α'_2 all by 0·01 reduces ΔH by 200 cal./mole, *i.e.*, 6%, and a by 8%, while b increases by 120%. The permissible variation or random error appears to vary with the form of the specific rotation–temperature curve and with the way in which the points enter into the solution, but in the cases studied accuracy to 0·01° seems to ensure a solution, whilst when the optical rotations are accurate only to 0·1° there is little chance of a result. Probably the percentage error is the better criterion, the figures being *ca.* 0·05 and 0·5%, respectively.

The way in which ΔH varies with a and b can be shown artificially by assuming errors in p', q', and z' of the solution so as to give, for the example with $\Delta H = -1624$ cal./mole and $a = 108$, with new values $a = 1000$, and $a = 10{,}000$; the values $b = -11{\cdot}7$ and $-12{\cdot}3$, $\Delta H = -1073$ and -908, respectively, are obtained. Thus variation by a factor of 100 in a produces variation by a factor of 2 in ΔH, which is consonant with their logarithmic relationship. Since a and b tend to have rather arbitrary values as a result of random errors in the curve of α against temperature this method may have greater value in the determination of ΔH than of a and b. Where results of sufficient accuracy are available, this method does make possible a true analysis of the rotatory dispersion. In fact, an analysis of a rotatory dispersion in terms of the Drude equation can only be considered to be of fundamental value when the large variations of rotation with temperature, due to the existence of the various isomeric forms, have been eliminated.

Scope of the Method.—Bernstein and Pedersen [3] have treated the rotatory power of *sec.*-butyl alcohol as that of a mixture of three forms due to rotational isomerism about a single bond, the observed value being that due to an equilibrium mixture of these three forms which are assumed to have quite different rotatory powers. This theory apparently leads to the rather surprising conclusion [4] that simple compounds of this type should not exhibit rotatory power in the absence of rotational isomerism. Although it is difficult to accept this conclusion, in view of this and other work on rotational isomerism of molecules containing an asymmetric group joined to a hydrocarbon skeleton by a single bond, any calculations relating variations of rotatory power with temperature to the proportions of various forms should be based on at least three such forms. The present work shows that complexity renders the success of such a calculation unlikely since whilst the solution of the " two-form " equation appears to depend on the smoothness of the curve of $(d\alpha/dT)/T$, in the " three-form " equation the corresponding criterion will be the smoothness of $[d^2\alpha/(d\lambda \,.\, dT)]/T$ which is much more critical. It is doubtful whether any measurements at present available are accurate enough.

The expression for two forms in equilibrium can thus obviously only be rigidly applied in the absence of rotational isomerism due to the presence of single bonds It should also be applicable to those systems (*a*) which consist of isomers of two groups widely separated

[3] Bernstein and Pedersen, *J. Chem. Phys.*, 1949, **17**, 885.
[4] *Idem, ibid.*, p. 888.

in terms of energy, and (*b*) in which one form is a ring structure with a relatively large rotatory power and the other a mixture of open-chain rotational isomers for which $d[\alpha]/dT$ will be small.

2 : 3-*Epoxypropyl Phenyl Ether.*—The "two-form" equation can be used for 2 : 3-epoxypropyl phenyl ether since this ether exhibits considerable variation of rotatory power with temperature, and its rotatory dispersion can be explained in terms of the suggested ring formation.[5] Thus, analysis of optical rotation–temperature curves should provide information on the energy difference between the two forms and enable the dispersion to be simplified.

The results, when reported previously,[6] were rounded off so as to be well within the experimental error, with consequent loss of vital accuracy. The original results are therefore given in Table 1. The individual experimental error represents $2\frac{1}{2}$ units in the second decimal place for the 5780 and 5461 Å lines and rather more than twice that figure for the other two. The mean experimental error should be rather less than this. Temperatures were read to 0·1° so that, in terms of absolute temperature, this accuracy is comparable with that of the polarimetric readings.

There is no difficulty in obtaining solutions for the 5780, 5461, and 4358 Å curves from the values given in Table 1 together with interpolated values (Table 2). The plot of specific rotation against temperature for light of wavelength 5086 Å showed that the results were not sufficiently accurate. For the 6438 Å line the 353·16° K point is probably in error; interpolation between 334·16° K and 371·16° K for this curve gives varying results some of which are quoted. Apart from these variations it is interesting to note that changes in interpolation of α_4 from 11·75° to 11·775° and α'_3 from 12·56° to 12·585° result in the change of *a* from 45 almost to infinity, the solution being unstable at this point, whilst with $\alpha_4 = 11{\cdot}80°$ and $\alpha'_3 = 12{\cdot}61°$ the solution is imaginary. Attempts to obtain suitable values as a basis for calculation are therefore useless, and the justification of the method lies in the agreement or otherwise of the results obtained directly from the experimental values. However,

TABLE 1. *Observed and calculated specific rotatory powers of* 2 : 3-*epoxypropyl phenyl ether.* [The calculated values, given as differences, were obtained by using the values $\Delta H = -2625$ cal./mole and (*a*) $\Delta S = -8{\cdot}3$ e.u./mole or (*b*) $\Delta S = -8{\cdot}6$ e.u./mole.]

T°, K		Wavelength, Å				
		6438	5780	5461	5086	4358
298·7		19·53	24·04	26·86	31·09	43·55
	(*a*)	−0·86	−0·01	−0·10	−0·18	−0·32
	(*b*)	−0·09	−0·40	+0·58	+0·43	−0·02
315·9		16·69	20·82	23·49	26·98	37·20
	(*a*)	−0·28	−0·02	−0·31	−0·23	−0·09
	(*b*)	−0·01	−0·54	−0·01	−0·00	−0·01
334·2		14·13	17·75	19·82	22·83	31·32
	(*a*)	0·00	0·00	0·00	+0·01	0·00
	(*b*)	0·00	−0·60	−0·01	−0·01	0·00
353·2		11·76	14·98	16·70	19·58	25·95
	(*a*)	+0·29	0·00	+0·06	−0·36	+0·10
	(*b*)	+0·08	−0·62	−0·16	−0·46	+0·11
371·2		10·37	12·71	14·26	16·35	21·76
	(*a*)	0·00	0·00	−0·01	0·00	−0·01
	(*b*)	−0·37	−0·60	−0·36	−0·22	+0·07
414		—	7·9	8·3	—	11·9
	(*a*)	—	+0·6	+1·3	—	+1·8
	(*b*)	—	+0·1	+0·8	—	+2·2
447		—	5·3	5·5	—	6·8
	(*a*)	—	+0·8	+1·4	—	+2·3
	(*b*)	—	+0·5	+0·9	—	+4·6

it is reasonable to eliminate results which can be shown to be improbable. The values obtained for the two highest temperatures are useful in this way though they are not

[5] Hargreaves, Thesis, London, 1949.
[6] Balfe, Hargreaves, and Kenyon, *J.*, 1950, 1861.

accurate enough to be used in the solution itself. Thus values over 5·5 for b at 5461 Å can be eliminated. It is more difficult to obtain an upper limit for a, but the calculated plot of α against T for $\Delta H = -2625$ cal./mole shows that the curvature becomes reversed below *ca.* 270° K. The increased slope between 315° and 270° K will be more than balanced by the reversed curvature below that temperature so that it is reasonable to use values at room

TABLE 2. *Calculated constants for 2 : 3-epoxypropyl phenyl ether.* (α_4 and α'_3 are interpolated values from Table 1.)

		Specific rotations [(+)-isomer]					
Wavelength	n =	1	2	3	4		
6438 (*a*)	α_n	+19·53°	+16·69°	+14·13°	+11·75°	$\Delta H = -3416$,	$\Delta S = -12·05$
	α'_n	19·53	16·69	12·56	10·37	$a = 45·21$, $b = 0·63$	
(*b*)	α_n	19·53	16·69	14·13	11·77	$\Delta H = -3194$,	$\Delta S = -11·07$
	α'_n	19·53	16·69	12·58	10·37	$a = 41·32$, $b = 1·493$	
(*c*)	α_n	19·52	16·68	14·13	11·77	$\Delta H = -1624$,	$\Delta S = -7·72$
	α'_n	19·52	16·68	12·58	10·37	$a = 108·0$, $b = -6·004$	
5780	α_n	24·04	20·82	17·75	14·62	$\Delta H = -2625$,	$\Delta S = -8·30$
	α'_n	24·04	20·82	15·75	12·71	$a = 47·56$, $b = -6·04$	
5461	α_n	26·86	23·49	19·82	16·29	$\Delta H = -5229$,	$\Delta S = -15·90$
	α'_n	26·86	23·49	17·52	14·26	$a = 36·19$, $b = 5·63$	
4358	α_n	43·55	37·20	31·32	25·28	$\Delta H = -3833$,	$\Delta S = -11·89$
	α'_n	43·55	37·20	27·42	21·76	$a = 73·38$, $b = 0·5654$	

The negative sign of ΔH (in cal./mole) and ΔS (in e.u./mole) indicates that the roots of the equation have been taken so that form A is the low-temperature form.

The temperatures corresponding to the rotations are:

n	1	2	3	4
T_n	298·66°	315·91°	334·16°	355·90°
T'_n	298·66	315·91	347·65	371·16

temperature together with an expression, $[\alpha] = a + cT$, to obtain a rough upper limit for a. This method is only justifiable if the inflexion point is near to room temperature; it seems reasonable to eliminate the value for a at 6438 Å, $\Delta H = -1624$ cal./mole, on this ground. The solution giving $\Delta H = -5229$ cal./mole can also be eliminated because of the unsuitability of the corresponding value of a and b.

The values of ΔS are determined by those obtained for ΔH, a, and b. This is one of the factors militating against an averaging of results. The solution of equation (1) gives a and b for one wavelength; the values at other wavelengths may be obtained from the corresponding ΔH and ΔS values, any pair of temperatures being used. The rotatory

TABLE 3. *Dispersions of "constants" a and b, derived from the following values.*

		A		*B*		*C*		*D*	
ΔH (calc./mole)		−2625		−2625		−3194		−3600	
ΔS (e.u.)		−8·3		−8·6		−11·07		−11·8	
λ	Series	*a*	*b*	*a*	*b*	*a*	*b*	*a*	*b*
6438	1	40·29	−6·98	41·98	−4·96	41·28	1·53	35·63	1·24
	2	37·17	−6·85	41·31	−4·38	33·66	6·22	35·38	1·57
	3	36·41	−3·65	38·86	−2·71	44·62	1·79	34·46	2·00
5780	1	47·58	−6·01	49·49	−3·72	48·69	3·63	42·29	3·30
	2	47·78	−6·21	50·35	−5·45	41·17	8·27	43·24	2·68
	3	47·62	−6·08	50·89	−4·72	58·62	1·20	44·98	1·50
5461	1	51·41	−4·51	53·50	−2·19	52·67	5·50	45·96	5·16
	2	55·72	−8·82	58·78	−6·72	47·82	8·48	50·29	1·81
	3	52·77	−6·47	56·38	−5·08	64·91	1·57	49·91	1·87
5086	1	61·14	−7·27	63·58	−4·34	62·56	5·04	54·39	4·62
	2	63·43	−9·27	66·89	−7·18	54·49	10·01	57·28	2·46
	3	61·24	−7·81	65·44	−6·19	75·38	1·56	57·90	1·91
4358	1	89·97	−15·72	93·74	−11·19	92·18	3·30	79·55	2·66
	2	88·84	−14·58	93·75	−11·20	76·19	13·16	80·14	2·47
	3	87·98	−13·89	94·19	−11·50	108·85	−0·07	83·05	0·46

Series 1 were calculated from values at 298·7° and 315·9°, series (2) from values at 315·9° and 334·2° and (3) from values at 334·2° and 371·2° K. Column *D* was calculated for a mean of the higher values from Table 2.

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dispersions of a and b determined for three pairs of temperatures and four values of ΔH are given in Table 3.

The nature of these dispersions may help in selection of the possible values of ΔH; but in this case the dispersions are not accurate enough to permit an unambiguous selection. However, when $1/a$ is plotted against λ^2 (the rough test for *simple* dispersion), a straight line is produced as in the plot of $1/[\alpha]$ against λ^2. But the plot of $1/b$ against λ^2 is markedly curved except for the values $\Delta H = -3194$, $\Delta H = -2625$ cal./mole, and $\Delta S = -8{\cdot}6$ e.u./mole). Of these the first and the last give the best agreement with a linear plot. In the first case the intercept on the wavelength axis, corresponding to $\lambda_0^2 = 0{\cdot}007$ ($\lambda_0 = 800$ Å) in the one-term Drude equation, is identical for a and b and is equal to that given by the $1/[\alpha]$–λ^2 plot. This implies an identity of the dispersions of a, b, and $[\alpha]$, as would be expected if the dispersion of each form were truly simple since in this case the rotation constant does not affect the dispersion but only the magnitude of the rotation. If, however, the dispersions are only pseudo-simple, as the value of λ_0 shows them to be, then λ_0 can vary even when the isomers are chemically identical, since the relative values of the different rotation constants of the Drude equation will affect the dispersion. Thus the linearity of the plot is not an absolute criterion, though other things being equal the simpler plot is naturally to be preferred.

The intercepts of the $1/a$–λ^2 plot for the first and the last case above correspond, whilst the intercept of the $1/b$–λ^2 plot corresponds to an absorption wavelength of 2200 Å. Since the dispersion of each form seems to be complex, other series showing a maximum in b may equally be correct, though it is likely that this maximum is in fact due to experimental error. Thus, examination of the dispersion here gives little help in selecting possible values of ΔH.

Greater assistance is obtainable from the study of the rotatory dispersion of 2 : 3-epoxypropyl phenyl ether in *n*-butyl ether.[6] It is clear from this that if the proposed explanation of the dispersion is to be maintained b should now have a negative value greater than 3·2 for the 4358 Å line. Thus the value $\Delta H = -2625$ cal./mole is preferred to $\Delta H = -3194$ cal./mole which also gives too large a value for b. From the values of Table 3, set A, rotatory powers were calculated for the whole field of observation; the differences from the observed values are given in Table 1, series (*a*). A satisfactory fit is obtained up to 373° K but above that the fit is not good. An attempt to improve this fit by inserting in equation (1) the value of α_{5461} at 447° K gives a new value for ΔS; a and b were then recalculated for each wavelength (Table 3, set B) and the figures given in Table 1, series (*b*), then obtained. Again the fit is not good at higher temperatures, the differences being outside the limit of probable error, but a better plot is obtained for the dispersion. Further fitting of the expressions to the experimental values might yield a better correlation, but the orders of magnitude are correct so that there is little doubt as to the essential validity of the results.

Thus a difference in heat content between the two postulated forms of the order of 2·5—3 kcal./mole gives the best fit to the dispersion. It has been suggested [5] that one form of 2 : 3-epoxypropyl phenyl ether is a ring structure. This ring structure (having a heat content 2·5—3 kcal./mole less than the open form) may be considered in the light of the rearrangement of phenyl allyl ether [7] and the suggestion of the ethylenic character of the epoxide ring.[8,9] It may be noted, however, that at 174° C the proportion of the ring form of 2 : 3-epoxypropyl phenyl ether is reduced to *ca.* 20%. It is not surprising, therefore, that the ether does not rearrange even at its boiling point when heated in nitrogen.

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[7] Tarbel, *Chem. Reviews*, 1940, **27**, 495.
[8] Walsh, *Nature*, 1947, **159**, 165.
[9] Linnett, *ibid.*, 1947, **160**, 162.

211. *Spectrophotometric Determination of the Dissociation Constant of Hydrogen Peroxide.*

By S. S. Muhammad and T. Navaneeth Rao.

The ultraviolet absorption spectra of hydrogen peroxide have been determined in aqueous buffers of different pH by spectrophotometry. The value $(2{\cdot}63 \pm 0{\cdot}12) \times 10^{-12}$ at 30° for the dissociation constant of hydrogen peroxide has been derived.

Aqueous solutions of hydrogen peroxide absorb continuously [1] in the range 3750—2150 Å, the extinction being a maximum at 2150 Å but decreasing continuously at longer wavelengths. Progressive addition of sodium hydroxide to aqueous hydrogen peroxide strongly displaces the absorption curves towards longer wavelengths.[2] This indicates that at a particular wavelength the optical density of hydrogen peroxide solution increases with increasing amounts of added alkali, pointing to a relation between optical density and pH. Our results confirm the observation by Bredig and his coworkers [2] and also lead to the conclusion that the optical density of aqueous hydrogen peroxide depends on the proportions of the molecular form H_2O_2 and of the anion HO_2^-: $H_2O_2 + H_2O = H_3O^+ + HO_2^-$.

By measuring the molar extinction coefficients at a given wavelength in acid solution (ε_1), alkaline solution (ε_3), and buffer solution (ε_2) of known pH, it is possible to calculate the value of pK from the equation [3] $pK = pH + \log_{10}[(\varepsilon_2 - \varepsilon_3)/(\varepsilon_1 - \varepsilon_2)]$. When all measurements are carried out with the same cell and solutions of the same concentration, the optical density or absorbance values can be used in place of molar extinction coefficients.

In Stenström and Goldsmith's method,[4] adopted by us, the use of the above equation is simplified by plotting absorbance against pH. At the midpoint of the break in the curve pH = pK, since at this point the log term is zero.

Experimental

The absorption spectra were measured with a Unicam quartz photo-electric spectrophotometer (Model SP 500) and a hydrogen lamp operated from a stabilised power supply. Both cells, of fused silica and of 1 cm. optical path, matched perfectly. pH measurements were taken with a Leeds and Northrup pH indicator having a glass electrode which was previously standardised.

Phosphate buffers (pH 2·0—12) were made up from solutions of 0·1M-phosphoric acid in 0·1N-potassium hydroxide. 0·1N-Potassium hydroxide solution was used as a solution of pH 13. All reagents were Merck's analytical grade.

All measurements were carried out at 30° ± 0·5° (room temperature).

Hydrogen peroxide (Merck) was purified by two distillations under reduced pressure. The concentration of the aqueous distillate was measured photometrically with use of a Beer's law graph obtained for the system H_2O_2–$Ti(SO_4)_2$.[5] The distillate was then diluted with conductivity water to give a 0·04M-solution. 1 c.c. of this was diluted to 25 c.c. with the buffer of known pH; thus the hydrogen peroxide concentration for absorption measurements was $1{\cdot}6 \times 10^{-3}$M. Solutions for use in the blank cell of the spectrophotometer contained 24 c.c. of buffer and 1 c.c. of water.

Fig. 1 contains the plots against wavelength of the absorbance of hydrogen peroxide in

[1] Urey, Dawson, and Rice, *J. Amer. Chem. Soc.*, 1929, **51**, 1371; Allmand and Style, *J.*, 1930, 596.
[2] Bredig, Lehman, and Kuhn, *Z. anorg. Chem.*, 1934, **218**, 16.
[3] Hammett, Dingwall, and Flexser, *J. Amer. Chem. Soc.*, 1935, **57**, 2103.
[4] Stenström and Goldsmith, *J. Phys. Chem.*, 1926, **30**, 1683; see also DeVries and Gantz, *J. Amer. Chem. Soc.*, 1954, **76**, 1008.
[5] Snell and Snell, "Colorimetric Methods of Analysis," Van Nostrand, New York, 1949, p. 882.

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solutions of pH 5·95, 11·23, 11·80, and 13·00. Beyond 2600 Å the absorption drops to very low values in dilute solutions.

The plot of absorbance against pH (not shown) at 2200 Å gives $pK = 11{\cdot}40$.

To reduce the absorbance to zero ionic strength, corrections were made in the apparent or measured pH of the buffers by using the relation $(pH)_0 = (pH)_a + 0{\cdot}51\,\mu^{\frac{1}{2}}/(1 + \mu^{\frac{1}{2}})$, where $(pH)_0$ is the pH of the buffer at zero ionic strength, $(pH)_a$ the apparent or measured pH of the same and μ is the ionic strength. The Table contains the compositions, ionic strengths, and corrected pH values of the buffers used.

Composition (mmoles)						Composition (mmoles)					
$(pH)_a$	H_3PO_4	KOH	$\mu^{\frac{1}{2}}$	$\frac{0{\cdot}5\mu^{\frac{1}{2}}}{1+\mu^{\frac{1}{2}}}$	$(pH)_0$	$(pH)_a$	H_3PO_4	KOH	$\mu^{\frac{1}{2}}$	$\frac{0{\cdot}5\mu^{\frac{1}{2}}}{1+\mu^{\frac{1}{2}}}$	$(pH)_0$
4·44	49·90	50·10	0·2243	0·0935	4·53	9·00	33·35	66·65	0·3161	0·1225	9·12
5·95	48·08	51·92	0·2361	0·0974	6·05	10·50	32·26	67·74	0·3262	0·1255	10·63
7·10	38·47	61·53	0·2909	0·1150	7·22	11·23	29·44	70·56	0·3514	0·1326	11·36
7·70	35·21	64·79	0·3072	0·1199	7·82	11·80	25·00	75·00	0·3874	0·1424	11·94
8·25	34·02	65·98	0·3130	0·1215	8·37	13·00	—	100·00	0·3162	0·1201	13·12

FIG. 1.

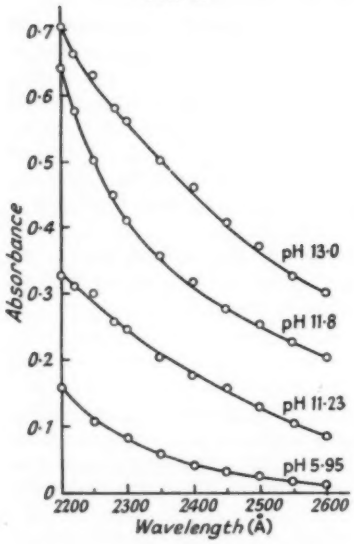
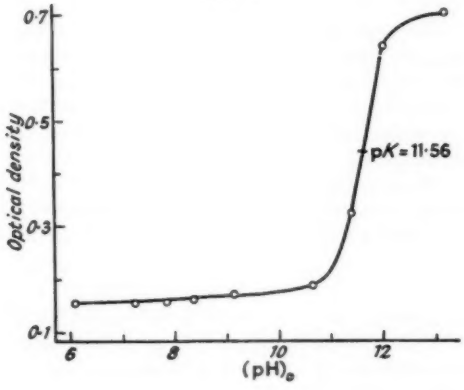


FIG. 2.



The plot of absorbance (Fig. 2) against these corrected pH values gives pK_a as 11·56 at 2200 Å. Similar treatment of results at 2220 and 2250 Å gives the pK values 11·58 and 11·60. The mean of these three is 11·58, which corresponds to a value of $K = (2{\cdot}63 \pm 0{\cdot}12) \times 10^{-12}$ at $30 \pm 0{\cdot}5°$ and shows fair agreement with the value of $(2{\cdot}82 \pm 0{\cdot}1) \times 10^{-12}$ at 30° obtained by Evans and Uri from an E.M.F. method.[6]

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[6] Evans and Uri, *Trans. Faraday Soc.*, 1949, **45**, 224.

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212. *Alkyl Migration in Some Organophosphorus Amidates.*

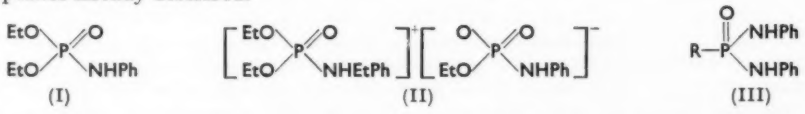
By J. I. G. Cadogan.

The decompositions of some organophosphorus amidates at high temperatures have been studied. The alkyl esters of the phosphoramidic and phosphonamidic acids which have been examined give tertiary amines. *P*-Alkyl-*NN'*-diphenylphosphonodiamidates, alone, are stable, but react vigorously with trialkyl phosphates to give high yields of dialkylanilines.

Several examples of the alkylation of amines by esters of phosphoric acid have been reported. Billman *et al.*[1] noted that trialkyl phosphates and substituted anilines, at the boiling point, gave high yields of the corresponding dialkylaniline and a mixture of phosphoric acids, this mixture indicating that each alkyl group of the ester took part in the reaction. Rueggburg and Chernack [2] later observed that morpholine is similarly alkylated at 150°. It is reasonable to suppose that the reaction involves nucleophilic attack by the amine on the α-carbon atom of the ester to give the monoalkylaniline, which, in turn, is further alkylated by the same mechanism.

In contrast to the above type of reaction, those described in this paper involve compounds containing ester and P–N–C groups in the same molecule, *e.g.*, the *N*-substituted dialkyl phosphoramidates, *e.g.*, (I). Amides of this type are not basic under normal conditions, neither are they strong nucleophils towards α-carbon atoms, but it is evident from the results described below that at high temperatures (*ca.* 250°) the nitrogen atom can be induced to attack the α-carbon atoms of ester groups in a manner similar to the reaction of aniline with trialkyl phosphates.

Diethyl *N*-phenylphosphoramidate (I), at the boiling point, decomposes very vigorously in about 30 sec. to give diethylaniline (85%) and ethylaniline (5%), both amines being partially bound as the salts of oxyacids of phosphorus. It is believed that the first step in the decomposition of the amidate involves the nucleophilic attack of the nitrogen atom on an ester group, to give ethylaniline, probably by way of the decomposition of an intermediate salt of the type (II). The secondary amine formed by this decomposition can then undergo alkylation by attacking any ester group, as in reaction of anilines and trialkyl phosphates already described.[1]



(I) (II) (III)

In parallel experiments it was shown that ethylaniline reacts with either triethyl phosphate or diethyl hydrogen phosphate to give diethylaniline; it is therefore not surprising that such a small amount of ethylaniline appears among the products of the decomposition of diethyl *N*-phenylphosphoramidate. The presence of such amounts of secondary amine was demonstrated by infrared analysis, using the strong band at 2·95 μ, which is attributed to the >NH group. All diethylaniline–ethylaniline mixtures obtained in the experiments described below were subjected to analysis of this kind, and the presence of diethylaniline was confirmed in each case by the preparation of *NN*-diethyl-*p*-nitrosoaniline.

The results described above are at variance with those of Gerrard and Jeacocke,[3] who stated that distillation of diethyl *N*-phenylphosphoramidate gave ethylaniline. No infrared evidence was however presented, and this conclusion was based on the melting point (136°) of a picrate of the basic product. It may be noted that the picrates of ethylaniline and

[1] Billman, Radike, and Mundy, *J. Amer. Chem. Soc.*, 1942, **64**, 2977; Billman, Davis, and Thomas, *ibid.*, 1946, **68**, 895.
[2] Rueggburg and Chernack, *ibid.*, 1948, **70**, 1802.
[3] Gerrard and Jeacocke, *Chem. and Ind.*, 1954, 1538.

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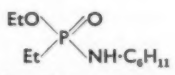
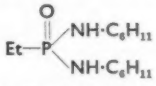
diethylaniline have similar melting points (132° and 142°) and cannot, in this case, be considered satisfactory for diagnostic purposes.

The postulated mechanism is supported by experiments with *P*-alkyl-*NN'*-diphenylphosphonodiamidates (III; R = Me and Et). These compounds contain the amidate function but no ester α-carbon atom, and self-alkylation is therefore impossible: the compounds are indeed stable. On admixture with trialkyl phosphates, however, rapid alkylation takes place at 250° to give high yields of dialkylanilines. Diphenyl *N*-phenylphosphoramidate also has no α-carbon atoms available for attack by nucleophilic centres and was found to be stable, as expected: in the presence of tri-*n*-butyl phosphate at 260°, it reacts slowly, to give a mixture of di-*n*-butylaniline and *n*-butylaniline (10% of the mixture).

The *N*-alkyl analogues which have been studied are more stable; whether this is a result of lower reaction temperatures (the boiling point of the material) or not has not been ascertained. Ethyl *P*-ethyl-*N*-*cyclo*hexylphosphonamidate (IV), after 90 min. at 230°, gave *N*-ethyl*cyclo*hexylamine (27%), *NN*-diethyl*cyclo*hexylamine (13%), and *P*-ethyl-*NN'*-di*cyclo*hexylphosphonodiamidate (V) (4%). The last-named compound is presumed to have arisen by disproportionation of the original amidate. It will be noted that ethyl

(IV)   (V)

P-ethyl-*N*-*cyclo*hexylphosphonamidate (IV) has only one ester group available for nucleophilic attack. It follows therefore that the length of the reaction chain will be less than if the corresponding phosphoramidate were used, and a correspondingly larger amount of P–N bonds will remain intact. This is supported by the isolation of *cyclo*hexylamine (28%) after acid hydrolysis of the residue from the decomposition.

The decompositions of diethyl *NN*-diethylphosphoramidate and ethyl *NNP*-triethylphosphonamidate were also studied. These compounds were the most stable encountered. The former was approximately half decomposed after 18 hr. at the boiling point, to give triethylamine and its salt with pyrophosphoric acid, while the latter, under the same conditions, gave triethylamine and a residuum of acids which could not be identified.

Experimental

All solids were recrystallised to constant m. p.

Diethyl NN-*diethylphosphoramidate*, a colourless oil (83%) obtained from diethyl phosphorochloridate (35 g.) and diethylamine (35 g.) in dry light petroleum (b. p. 40—60°; 250 ml.), had b. p. 106—108°/20 mm., n_D^{25} 1·4212 (Found: C, 46·2; H, 10·0. Calc. for $C_8H_{20}O_3NP$: C, 45·9; H, 9·6%).

Ethyl NNP-*triethylphosphonamidate*, b. p. 127—128°/25 mm., n_D^{25} 1·4368 (Found: C, 50·0; H, 10·2. $C_8H_{20}O_2NP$ requires C, 49·7; H, 10·4%), and *ethyl* P-*ethyl*-N-cyclo*hexylphosphonamidate*, m. p. 75°, colourless prisms from light petroleum (b. p. 40—60°) (Found: C, 54·9; H, 10·3. $C_{10}H_{22}O_2NP$ requires C, 54·8; H, 10·1%), were prepared in the same way from ethyl ethylphosphonochloridate and diethylamine and *cyclo*hexylamine respectively.

P-*Ethyl*-NN'-di*cyclohexylphosphonodiamidate*, m. p. 160°, colourless needles from acetone (Found: C, 61·7; H, 11·1. $C_{14}H_{29}ON_2P$ requires C, 61·7; H, 10·7%), was prepared from ethylphosphonic dichloride and an excess (10%) of *cyclo*hexylamine in dry benzene as described above. Similarly were obtained *P*-ethyl-*NN'*-diphenylphosphonodiamidate (m. p. 147°) and *P*-methyl-*NN'*-diphenylphosphonodiamidate (m. p. 157°), with the exception that the reactions were effected in dry chloroform solution and the products were recrystallised from aqueous ethanol.

Diphenyl *N*-phenylphosphoramidate [4] had m. p. 129—130°, and diethyl *N*-phenylphosphoramidate [5] had m. p. 96°.

Decomposition of Diethyl N-*Phenylphosphoramidate*.—The amidate (18·5 g.) was heated in an

[4] Foster, Overend, and Stacey, *J.*, 1951, 980.
[5] McCombie, Saunders, and Stacey, *J.*, 1945, 380.

oil-bath. At 260° a very vigorous reaction of about 30 sec. duration occurred, and two layers were formed. When cool they were separated. The top layer (6·7 g.) was distilled (b. p. 210—216°, n_D^{25} 1·5296), leaving no residue, and was shown to be a mixture of diethylaniline and ethylaniline (*ca.* 5% by infrared spectroscopy). A portion gave a good yield of *NN*-diethyl-*p*-nitrosoaniline, m. p. and mixed m. p. 84°. The bottom layer was a hard glass, insoluble in ether and soluble in water; its aqueous solution (pH 2) was extracted with ether to remove any soluble material but with a negative result; the aqueous layer was basified, giving an oil which was isolated by extraction. This gave a mixture (4·0 g.), b. p. 210—216°, n_D^{25} 1·5324, of diethyl- and ethyl-aniline of the same composition as that of the top layer. Thus were isolated diethyl- (85%) and ethyl-aniline (5%).

In a second experiment the bottom layer was dissolved in water and treated with silver nitrate solution to give a white precipitate. Its infrared spectrum indicated that it was a complex mixture of salts of oxyacids of phosphorus and was not identical with silver phosphate, metaphosphate, or pyrophosphate alone.

Decomposition of Ethyl P-*Ethyl*-N-cyclo*hexylphosphonamidate*.—The amidate (16 g.) was kept at 230—240° for 90 min. and then allowed to cool. The mixture, which consisted of a straw-yellow gummy solid with some supernatant liquid (1 ml.), was treated with water and extracted with ether. Evaporation of the ether layer left a residue (0·7 g.) which gave colourless needles (from acetone), m. p. 158°, not depressed on admixture with *P*-ethyl-*NN'*-di*cyclo*hexylphosphonodiamidate (m. p. 160°). The infrared spectra of the samples were identical.

The aqueous layer (pH *ca.* 2) from the above extraction was basified and extracted with ether. Working up of the extracts gave a colourless oil (4·0 g.), b. p. 170—180°, n_D^{25} 1·4501. Its infrared spectrum indicated the presence of both *NN*-diethyl*cyclo*hexylamine and a secondary amine (strong >NH band), and the absence of *cyclo*hexylamine. A portion of this distillate, gave a colourless methiodide (m. p. 238°, from acetone) which, from analyses, appeared to be N-*ethyl*-N-cyclo*hexyl*-NN-*dimethylammonium iodide* (Found: C, 42·1; H, 8·1. $C_{10}H_{22}NI$ requires C, 42·4; H, 7·8%). This suggested the presence in the original distillate of *N*-ethyl-*cyclo*hexylamine, which was confirmed by the formation of N-*ethyl*-N-cyclo*hexyl*-p-*toluenesulphonamide*, colourless plates, m. p. 104—105° (2·5 g. from 2·3 g. of distillate) (Found: C, 63·65; H, 8·4. $C_{15}H_{23}O_2NS$ requires C, 64·0; H, 8·2%). The water-insoluble oil (0·8 g.) also formed during the preparation of the sulphonamide was dissolved in chloroform and washed with alkali, then with water and dried. The product gave a methiodide, m. p. 224°, from acetone–light petroleum, undepressed on admixture with NN-*diethyl*-N-cyclo*hexyl*-N-*methylammonium iodide*, m. p. 224° (Found: C, 44·5; H, 8·4. $C_{11}H_{24}NI$ requires C, 44·5; H, 8·1%). The distillate therefore contained a mixture of *N*-ethyl- and *NN*-diethyl-*cyclo*hexylamine.

The aqueous fraction from the second ether-extraction described above was then examined. The solution was acidified and boiled for 15 min. When cool, it was basified and extracted with chloroform. Removal of the solvent left an oil, b. p. 137°, n_D^{25} 1·4561 (cf. *cyclo*hexylamine, n_D^{25} 1·4575). A portion of the base gave *N-cyclo*hexylphthalimide, m. p. and mixed m. p. 168—169° (Found: C, 73·4; H, 6·8. Calc. for $C_{14}H_{15}O_2N$: C, 73·3; H, 6·6%). In addition the infrared spectra of the free amine and *cyclo*hexylamine were identical.

Reactions between P-*Alkyl*-NN'-*diphenylphosphonodiamidates* (III) *and Trialkyl Phosphates*.—In each case the diamidate (1 mol.) with the trialkyl phosphate (2 mol.) was immersed in an oil-bath at 250°. A vigorous reaction soon ensued which subsided to gentle boiling after about 30 sec. The mixture, which then consisted of two liquid layers, was allowed to boil under reflux for a total of 10 min., and the layers were worked up separately. The top layer was pale yellow and was subjected first to infrared examination. In the experiments with triethyl phosphate this layer was shown to be diethylaniline, with no sign of the band at 2·95 μ (>NH). The top layer from the experiment with trimethyl phosphate was dimethylaniline, while that from the tri-*n*-butyl phosphate experiments consisted of di-*n*-butylaniline (90—95%) and *n*-butylaniline (5—10%). In another experiment involving tri-*n*-butyl phosphate, in which the time of boiling was increased to 1½ hr., no trace of *n*-butylaniline was detected spectroscopically in the products.

In each experiment the top layer was then dissolved in dilute acid and extracted with ether. The aqueous portion was basified, and the products were isolated by extraction with chloroform. They were distilled from zinc dust and their natures confirmed by the preparation of suitable derivatives, as described below.

The bottom layers of the reaction mixtures were all yellow gums. Their aqueous solutions

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were extracted with chloroform to remove any free base present, which was combined then with the top layer before it was distilled (see above). The aqueous part was basified to give further amounts of bases, which were distilled from zinc dust and subjected to infrared analysis for >NH content. The compositions of the mixtures from the bottom layers were identical with those from the top. The diethylaniline obtained from these experiments had b. p. 210—216°, n_D^{25} 1·5358—1·5394, and each sample gave *NN*-diethyl-*p*-nitrosoaniline, m. p. and mixed m. p. 84°. The dimethylaniline had b. p. 193°, n_D^{25} 1·5533, and gave *p*-bromo-*NN*-dimethylaniline, m. p. and mixed m. p. 53° (Found : N, 7·0. Calc. for $C_8H_{10}NBr$: N, 6·8%). The mixtures of di-*n*-butylaniline and *n*-butylaniline had b. p. 260—270°, n_D^{25} 1·5163—1·5170, and all gave di-*n*-butylaniline hydrochloride (from benzene–light petroleum), m. p. and mixed m. p. 156°, and di-*n*-butylaniline picrate, needles (from ether), m. p. and mixed m. p. 124—125° (Found : N, 12·7. Calc. for $C_{20}H_{26}O_7N_4$: N, 12·9%). The yields of amines produced in the reactions are given in the Table.

R in amidate (III)	R′ in $(R'O)_3PO$	Free amine (%)		Amine present as salt	
		Ph·NR′$_2$	Ph·NHR′	Ph·NR′$_2$	Ph·NHR′
Me	Et	39	0	59	0
Et	Et	32	0	64	0
Me	Bu^n	55	6	37	3
Et	Bu^n	41	4	24	*ca.* 1
Me	Me	46	0	25	0

Reaction of Diphenyl N-*Phenylphosphoramidate with Tri*-n-*butyl Phosphate.*—The amidate (4·3 g.) and the ester (7·0 g.) were kept at 250—260° for 1 hr. and then allowed to cool. The mixture was a homogeneous viscous liquid which was treated with an excess of aqueous alkali and extracted with ether. Working up of the extracts gave a mixture (2 g.) of di-*n*-butylaniline (90%) and *n*-butylaniline (10%), b. p. 260—270°, n_D^{25} 1·5170. The presence of the tertiary base was confirmed by the preparation of the picrate and the hydrochloride (constants given above).

Decomposition of Ethyl NNP-*Triethylphosphonamidate.*—The amidate (18 g.) was boiled under reflux for 18 hr. with moisture excluded, and then distilled to give triethylamine (6·2 g.) (methiodide, m. p. and mixed m. p. 293°), and leaving a brown water-soluble gum. This was dissolved in water and extracted with chloroform to remove any starting material. The aqueous layer was basified and extracted with chloroform. Evaporation of the extracts left a trace of a dark unidentified oil. The aqueous layer was evaporated to dryness and the mixture of sodium salts left was extracted with dry ethanol for 8 hr. Evaporation of the extracts left a white powder which appeared (infrared) to be a mixture of sodium salts of some oxyacids of phosphorus. The mixture could not be identified.

Decomposition of Diethyl NN-*Diethylphosphoramidate.*—The amidate (26 g.) was boiled under reflux with moisture excluded for 18 hr. The heterogeneous mixture was then separated, giving a dark liquid layer (10·7 g.) and a crystalline solid. The former gave triethylamine (1·4 g.; b. p. 89°; methiodide, m. p. and mixed m. p. 293°), starting material (8·8 g.; b. p. 115°/30 mm., n_D^{25} 1·4210), and a residue (0·4 g.) which could not be identified. The solid layer was insoluble in ether but dissolved readily in water to give an acid solution. A small portion (*ca.* 10%) of this solution gave a yellow precipitate with silver nitrate, which had an infrared spectrum identical with that of silver pyrophosphate. The main bulk was basified with sodium carbonate and extracted with chloroform. The extracts were dried and treated with methyl iodide. Evaporation left triethylmethylammonium iodide (3·5 g.), m. p. and mixed m. p. 293°.

In a second experiment, the solid component, in ethanol, was added to an ethanol solution of sodium ethoxide. The gelatinous precipitate was separated by use of the centrifuge, and the supernatant liquid was treated with methyl iodide to give triethylmethylammonium iodide. The gummy solid was triturated with a few drops of water to give a white solid, which had a spectrum identical with that of sodium pyrophosphate.

The microanalyses were carried out by Mr. F. E. Charlton and Mr. A. C. Thomas, and the infrared determinations are due to Mr. L. C. Thomas and Mr. M. J. Rumens, to all of whom thanks are offered. This investigation was carried out during the tenure of a Civil Service Senior Research Fellowship.

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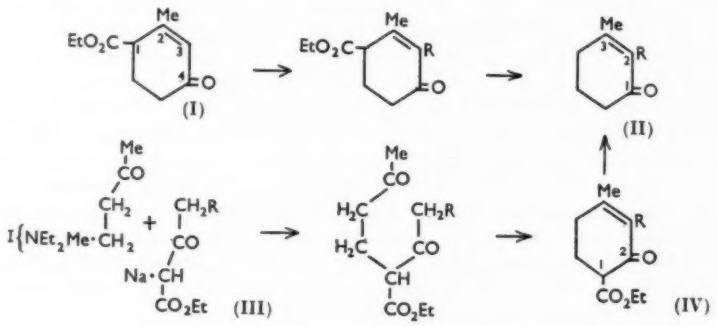
213. *Experiments on the Synthesis of the Pyrethrins. Part XII.** cyclo*Hexenone Analogues of Cinerone and Pyrethrone.*

By A. J. B. Edgar, S. H. Harper, and M. A. Kazi.

*cyclo*Hexenone analogues of cinerone and pyrethrone are prepared by alkylation of Hagemann's ester, ethyl 2-methyl-4-oxo*cyclo*hex-2-enecarboxylate. 2-Alkyl-4-bromo-3-methyl*cyclo*hex-2-enones could not be obtained by the action of *N*-bromosuccinimide, as aromatisation supervened. However, similar substitution of *iso*phorone (3 : 5 : 5-trimethyl*cyclo*hex-2-enone) gives the crystalline 4-bromo-ketone, converted into the 4-acetoxy- and 4-chrysanthemoyloxy-derivatives without rearrangement; however, alkaline hydrolysis is accompanied by rearrangement to 3 : 4 : 5-trimethylphenol. The chrysanthemic esters synthesised are not insecticidal.

This paper describes the preparation of a series of *cyclo*hexenone analogues of cinerone and pyrethrone and attempts to prepare similar analogues of pyrethrin-I, to discover the effect on insecticidal activity of replacing the *cyclo*pentenone by a *cyclo*hexenone ring.

Although individual members were prepared by lengthy ring closure procedures in the *cyclo*pentenone series,[1] the wider range of *cyclo*hexenone derivatives available suggested the use of a common cyclic intermediate. A suitable compound appeared to be Hagemann's ester (I), for earlier work indicated that alkylation of the sodio-derivative occurs in the 3-position. Subsequent hydrolysis and decarboxylation would give the 2-alkyl-3-methyl*cyclo*hex-2-enone (II; R = alkyl). However, the evidence that alkylation in ethanolic sodium ethoxide occurs in the 3-position is slender. Dieckmann [2] and



Kötz *et al.*[3] respectively oxidised the *iso*propyl and the methyl derivative (II) and obtained semicarbazones considered to be that of 5-oxohexanoic acid. Other evidence is that of Hogg [4] who alkylated Hagemann's ester with 3-methoxyphenethyl bromide, but in liquid ammonia with subsequent refluxing in toluene, and then by cyclisation and dehydrogenation, obtained 7-methoxy-1-methylphenanthrene.

As a preliminary to our use of Hagemann's ester we sought more direct proof that alkylation of the ester (I) in ethanolic sodium ethoxide occurs in the 3-position. Use of *cis*-crotyl chloride followed by hydrolysis and decarboxylation gave a ketone identical with that prepared by the Robinson–Mannich condensation [5] of 4-diethylaminobutan-2-one

* Part XI, *J.*, 1956, 3963.

[1] Crombie, Edgar, Harper, Lowe, and Thompson, *J.*, 1950, 3552.
[2] Dieckmann, *Ber.*, 1912, **45**, 2697.
[3] Kötz, Blendermann, Mähnert, and Rosenbusch, *Annalen*, 1913, **400**, 72.
[4] Hogg, *J. Amer. Chem. Soc.*, 1948, **70**, 161.
[5] du Feu, McQuillin, and Robinson, *J.*, 1937, 53.

methiodide with ethyl sodio-3-oxo-oct-6-enoate [6] (III; R = CH_2·CH:CHMe-*cis*), followed by cyclisation and decarboxylation. Substitution of the ester (I) had, therefore, occurred in the 3-position and the ketone had structure (II; R = CH_2·CH:CHMe-*cis*), being the analogue of *cis*-cinerone. Further, the structure and geometrical configuration of the allylic halide is retained in this alkylation, consistently with an S_N2 mechanism. Similarly, alkylation of Hagemann's ester with *trans*-crotyl chloride gave the isomeric *trans*-ketone. Alkylation in liquid ammoniacal sodamide occurs in the same position as in ethanolic sodium ethoxide, for the ketones obtained from Hagemann's ester and pentyl bromide in these two media were identical.

2-Allyl-3-methyl*cyclo*hex-2-enone, prepared by alkylation of Hagemann's ester with allyl chloride, was partially hydrogenated over palladised barium sulphate, giving 3-methyl-2-propyl*cyclo*hex-2-enone, which was also obtained from Hagemann's ester and propyl bromide. Alkylation of Hagemann's ester with pent-*trans*-2-enyl bromide gave 3-methyl-2-pent-*trans*-2′-enyl*cyclo*hex-2-enone, the analogue of *trans*-jasmone,[7] which however possessed a mimosa odour.

Synthesis of the *cyclo*hexenone analogues of *cis*- and *trans*-pyrethrone was effected with the same side-chain intermediates as had been employed for *cis*- and *trans*-pyrethrolone.[8,9] Alkylation of Hagemann's ester with pent-4-en-2-ynyl chloride gave 3-methyl-2-(pent-4-en-2-ynyl)*cyclo*hex-2-enone, which was hydrogenated over Lindlar's palladised calcium carbonate: the low intensity of ultraviolet absorption of the resulting diene-ketone ($\varepsilon_{max.}$ 17,200) indicates that, although the product was mainly 3-methyl-2-(penta-*cis*-2 : 4-dienyl)*cyclo*hex-2-enone, reduction was not fully selective as had been observed also with *cis*-pyrethrolone.[10] The ketone showed, *inter alia*, infrared bands at 10·05, 11·1, and 12·75(w) μ, characteristic of the alka-*cis*-2 : 4-dienyl group, previously observed in *cis*-pyrethrolone,[10] which precludes the *trans*-configuration for our ketone.

Alkylation of Hagemann's ester with pent-*trans*-2-en-4-ynyl chloride gave 3-methyl-2-(pent-*trans*-2-en-4-ynyl)*cyclo*hex-2-enone, but hydrogenation of this over palladised calcium carbonate (not Lindlar's catalyst) gave a diene-ketone whose ultraviolet absorption ($\varepsilon_{max.}$ 15,850) showed it to have low conjugated-diene content. A similar heterogeneous product was obtained by alkylation of Hagemann's ester with the chloride of penta-*trans*-2 : 4-dienol (prepared from pent-*trans*-2-en-4-ynol by hydrogenation). This lack of selectivity in the hydrogenation of the penta-*trans*-2-en-4-ynyl system was also observed in our earlier work on *trans*-pyrethrolone.[9] The use, however, of penta-*trans*-2 : 4-dienol, prepared by reduction of penta-*trans*-2 : 4-dienal with lithium aluminium hydride,[9] gave 3-methyl-2-(penta-*trans*-2 : 4-dienyl)*cyclo*hex-2-enone, whose ultraviolet light absorption (Figure) and that of its semicarbazone (Figure) showed it to be pure *trans*-diene-ketone. Consistently with this, the ketone formed an adduct with maleic anhydride which, however, tended to dissociate on recrystallisation.

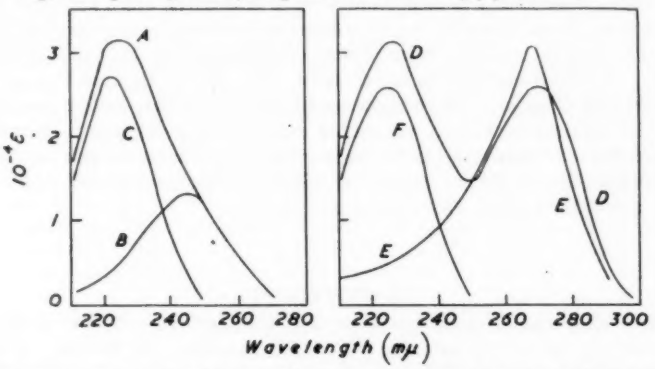
The 3-methyl*cyclo*hex-2-enones with a non-chromophoric 2-substituent absorb maximally, with one exception, within the wavelength limits (247 ± 5 mμ) predicted by Woodward [11] for trisubstituted αβ-unsaturated ketones (Table). However, the ketones containing a conjugated diene or enyne chromophore in the side chain absorb maximally at shorter wavelengths (225—234 mμ). In the case of 3-methyl-2-(penta-*trans*-2 : 4-dienyl)*cyclo*hex-2-enone this is due to superposition of the more strongly absorbing diene chromophore ($\lambda_{max.}$ *ca.* 223 mμ) on that of the enone chromophore ($\lambda_{max.}$ 245 mμ), as is shown in the Figure. Support for this is provided by the semicarbazone, for the absorption maxima of the C=C–C=C (*ca.* 225 mμ) and C=C–C=N (*ca.* 266 mμ) chromophores are sufficiently displaced for the absorption curve to be resolved into distinct maxima.

[6] Crombie, Harper, Stedman, and Thompson, *J.*, 1951, 2445.
[7] Crombie and Harper, *J.*, 1952, 869.
[8] Crombie, Harper, Newman, Thompson, and Smith, *J.*, 1956, 126.
[9] Crombie, Harper, and Thompson, *J.*, 1951, 2906.
[10] Crombie, Harper, and Newman, *J.*, 1956, 3963.
[11] Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 72, 76.

Crombie, Elliott, and Harper [12] used *N*-bromosuccinimide to convert 2-alkyl-3-methyl-*cyclo*pent-2-enones into the 4-bromo-ketones and thence by replacement into alkyl-rethrolones and their chrysanthemic esters. A similar series of reactions with 2-alkyl-3-methyl*cyclo*hex-2-enones could not be realised. In initial small-scale experiments 3-methyl- and 3-methyl-2-pentyl-*cyclo*hex-2-enone reacted smoothly with *N*-bromosuccinimide in the presence of benzoyl peroxide, but in all subsequent experiments either with or without benzoyl peroxide a brown colour developed which was followed by a rapid evolution of hydrogen bromide and a phenolic smell. Such a course of events would follow from elimination of hydrogen bromide from the 4-bromo-ketone, the resultant *cyclo*hexadienone passing into a phenol by enolisation.

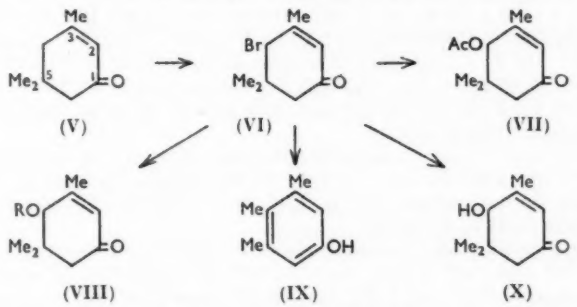
Attention was turned to the 5 : 5-disubstituted *cyclo*hex-2-enone, *iso*phorone (V), whose 4-bromo-derivative (VI) cannot lose hydrogen bromide directly. Reaction with *N*-bromosuccinimide yielded smoothly a stable crystalline monobromo-ketone, presumed

Light absorption of 3-*methyl*-2-(*penta*-trans-2 : 4-*dienyl*)cyclo*hex*-2-*enone*.



A, 3-*Methyl*-2-(*penta*-trans-2 : 4-*dienyl*)cyclo*hex*-2-*enone*. *B*, 3-*Methyl*-2-*pentyl*cyclo*hex*-2-*enone*. *C*, *Subtraction curve* (*A* — *B*) *equals the absorption of the diene chromophore in* 3-*methyl*-2-(*penta*-trans-2 : 4-*dienyl*)cyclo*hex*-2-*enone*. *D*, 3-*Methyl*-2-(*penta*-trans-2 : 4-*dienyl*)cyclo*hex*-2-*enone semicarbazone*. *E*, 3-*Methyl*-2-*pentyl*cyclo*hex*-2-*enone semicarbazone*. *F*, *Subtraction curve* (*D* — *E*) *equals the absorption of the diene chromophore in* 3-*methyl*-2-(*penta*-trans-2 : 4-*dienyl*)cyclo*hex*-2-*enone*.

to be 4-bromo*iso*phorone (VI) rather than the 6-bromo- or 3-bromomethyl isomer by analogy with the similar bromination of 2-alkyl-3-methyl*cyclo*pent-2-enones [12] and evidence below. An unstable liquid bromo-ketone was also formed but was not examined.



Replacement of bromine by acetoxyl was accomplished by use of silver acetate, without rearrangement, for the product (VII) formed a 2 : 4-dinitrophenylhydrazone and showed the light absorption of an αβ-unsaturated ketone. Similarly, treatment with silver

[12] Crombie, Elliott, and Harper, *J.*, 1950, 971.

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chrysanthemate gave the *iso*phorone ester (VIII; R = chrysanthemoyl). Alkaline hydrolysis, however, of 4-acetoxy*iso*phorone (VII) was accompanied by rearrangement, for the product was 3 : 4 : 5-trimethylphenol (IX), formed presumably by alkyl–oxygen fission of the ester, followed by Wagner–Meerwein rearrangement of the carbonium ion and aromatisation by enolisation. The formation of 3 : 4 : 5-trimethylphenol as the sole phenolic product confirms the conclusion that the crystalline monobromo-ketone is the 4-isomer. Hydrolysis of 4-bromo*iso*phorone with aqueous sodium carbonate gave a mixture of the phenol (IX) and a neutral product, assumed to be 4-hydroxy*iso*phorone (X), since its ultraviolet-light absorption (max. at 225 mμ; ε 9050) is that of an αβ-unsaturated ketone.

Treibs and Bast [13] showed that *cyclo*hexenes are acetoxylated at the α-methylene group when heated with mercuric acetate, with concomitant separation of metallic mercury. Attempts to acetoxylate *cyclo*hex-2-enones in the 4-position failed, although nearly quantitative separation of mercury occurred. 3-Methyl*cyclo*hex-2-enone and *iso*phorone gave traces of phenols, presumably *m*-cresol and 3 : 4 : 5-trimethylphenol respectively.

An attempt to prepare a 6-chloro- and a 6-hydroxy-ketone by a procedure similar to that used by LaForge and Soloway [14] for 2-butyl-5-hydroxy-3-methyl*cyclo*pent-2-enone was unsuccessful. 2-Allyl-3-methyl*cyclo*hex-2-enone (II; R = CH_2·CH:CH_2) gave the ester (IV; R = CH_2·CH:CH_2) in good yield on use of ethyl carbonate and sodium hydride, and the derived sodio-derivative was converted by toluene-*p*-sulphonyl chloride into the 1-chloro-ester, but acid hydrolysis failed to give the desired α-chloro-ketone.

The (±)-*trans*-chrysanthemic esters of 4-hydroxy*iso*phorone and 3 : 4 : 5-trimethylphenol were non-toxic to houseflies and mustard beetles.

Experimental

Hagemann's ester was prepared by Smith and Rouault's procedure [15] in 40% yield, but cooling the reactants to −5° (cf. Horning *et al.*[16]) increased the yield to 45%. Like Smith and Rouault, we could not reach the 71% yield reported by Bergmann and Weizmann.[17] The ester had b. p. 96—98°/0·3 mm., n_D^{20} 1·4850—1·4854.

Ethyl 3-*Alkyl*-2-*methyl*-4-*oxo*cyclo*hex*-2-*enecarboxylates*.—A typical preparation was as follows: Hagemann's ester (182 g., 1 mol.) was added during 30 min. to a stirred solution of sodium (23 g.) in absolute ethanol (800 ml.) cooled to room temperature. After a further 45 min. (to complete formation of the sodio-derivative) allyl chloride (76·5 g., 1 mol.) was added during 1 hr., and the mixture was stirred during another 2 hr. and refluxed for 3 hr. Most of the ethanol was removed in a vacuum, water added, and the oil extracted with ether. The dried extract ($MgSO_4$) was evaporated and distilled, to give *ethyl* 3-*allyl*-2-*methyl*-4-*oxo*cyclo*hex*-2-*enecarboxylate* (170 g., 80%), b. p. 108—109°/0·1 mm., 120—122°/0·6 mm., n_D^{20} 1·4950—1·4958, max. at 241 mμ (ε 11,000) (Found: C, 69·9; 70·1; H, 8·0, 8·4. $C_{13}H_{18}O_3$ requires C, 70·2; H, 8·15%). The 2 : 4-*dinitrophenylhydrazone* separated as deep red plates (from ethanol), m. p. 106° (Found: C, 57·2; H, 5·3. $C_{19}H_{22}O_6N_4$ requires C, 56·7; H, 5·5%).

The majority of the 3-alkyl-esters prepared were used for the next stage without isolation, but the following were characterised:

Ethyl 3-*butyl*-2-*methyl*-4-*oxo*cyclo*hex*-2-*enecarboxylate* (from butyl bromide) (66%), b. p. 110—117°/0·1 mm., n_D^{20} 1·486 (Found: C, 70·3; H, 9·8. $C_{14}H_{22}O_3$ requires C, 70·6; H, 9·9%). The *semicarbazone* formed needles, m. p. 121°, from ethanol (Found: C, 60·7; H, 8·4. $C_{15}H_{25}O_3N_3$ requires C, 61·0; H, 8·5%).

Ethyl 3-*but*-cis-2′-*enyl*-2-*methyl*-4-*oxo*cyclo*hexenecarboxylate* (from *cis*-crotyl chloride [6]) (70%), b. p. 120—122°/0·5 mm., n_D^{20} 1·4982, max. at 241 mμ (ε 10,350) (Found: C, 71·9; H, 8·8. $C_{14}H_{20}O_3$ requires C, 71·1; H, 8·5%), and the trans-*analogue* (from *trans*-crotyl bromide [1])

[13] Treibs and Bast, *Annalen*, 1949, **561**, 165.
[14] LaForge and Soloway, *J. Amer. Chem. Soc.*, 1947, **69**, 2932.
[15] Smith and Rouault, *J. Amer. Chem. Soc.*, 1943, **65**, 631.
[16] Horning, Denekas, and Field, *J. Org. Chem.*, 1944, **9**, 547.
[17] Bergmann and Weizmann, *J. Org. Chem.*, 1939, **4**, 267.

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(89%), b. p. 116—117°/0·1 mm., n_D^{20} 1·4982 (Found: C, 70·9; H, 8·8%) [2 : 4-*dinitrophenylhydrazone*, orange-red needles (from ethanol), m. p. 119—120° (Found: C, 58·5; H, 5·9. $C_{20}H_{24}O_6N_4$ requires C, 57·7; H, 5·8%)].

Ethyl 3-but-2′-ynyl-2-methyl-4-oxo*cyclo*hex-2-enecarboxylate (from but-2-ynyl chloride [6]), b. p. 118—121°/0·1 mm., n_D^{20} 1·507 [prepared with Mr. R. E. Stedman].

*Ethyl 2-methyl-4-oxo-2-pentyl*cyclo*hex-2-enecarboxylate* (from pentyl bromide) (62%), b. p. 120—123°/0·05 mm., n_D^{20} 1·4842 (Found: C, 70·8; H, 9·4. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%) [2 : 4-*dinitrophenylhydrazone*, orange needles (from ethanol), m. p. 72° (Found: C, 58·4; H, 6·5; N, 13·3. $C_{21}H_{28}O_6N_4$ requires C, 58·3; H, 6·5; N, 13·0%)]. [When prepared in liquid ammonia by Hogg's procedure [4] the keto-ester (31%) had b. p. 120—130°/0·3 mm., n_D^{20} 1·4835, and the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 72° (Found: C, 58·7; H, 6·6; N, 12·7%).]

Ethyl 2-methyl-4-oxo-2-(pent-trans-2-*en*-4-*ynyl*)cyclo*hex-2-enecarboxylate* (from pent-*trans*-2-en-4-ynyl chloride,[9] b. p. 80—83°/190 mm., n_D^{25} 1·489) (55%), b. p. 125—127°/10^{-3} mm., n_D^{20} 1·5239 (Found: C, 71·1; H, 7·4. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%) [*semicarbazone*, prisms (from ethanol or 2-methoxyethanol), m. p. 141—142° (Found: C, 63·1; H, 7·1. $C_{16}H_{21}O_3N_3$ requires C, 63·3; H, 7·0%)].

*2-Alkyl-3-methyl*cyclo*hex-2-enones*.—A typical preparation was as follows: Ethyl 3-allyl-2-methyl-4-oxo*cyclo*hex-2-enecarboxylate (111 g.) was heated under reflux with 15% ethanolic potassium hydroxide (250 ml.) during 8 hr. Next day most of the solvent was distilled off and the residue diluted with ice-water (200 ml.). After acidification with dilute hydrochloric acid the mixture was heated to 50° during 1 hr. (to bring about decarboxylation), then cooled, and the product was isolated with ether. Distillation gave *2-allyl-3-methyl*cyclo*hex-2-enone* (48 g., 64%), having a floral odour, b. p. 65—66°/0·05 mm., n_D^{20} 1·5050, for light absorption see the Table (Found: C, 79·4, 79·6; H, 9·55, 9·5. $C_{10}H_{14}O$ requires C, 79·9; H, 9·4%). The *semicarbazone* separated as needles (from ethanol), m. p. 172—173°, for light absorption see the Table (Found: C, 63·9; H, 8·2. $C_{11}H_{17}ON_3$ requires C, 63·7; H, 8·3%). There was a 12% recovery of unhydrolysed keto-ester, b. p. 112—116°/0·2 mm., n_D^{20} 1·498.

*Ultraviolet light absorption of 2-alkyl-3-methyl*cyclo*hex-2-enones in ethanol.*

	Ketones		Semicarbazones	
Alkyl	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε
2-Propyl	242	12,900	—	—
2-Allyl	242	12,450	269 *	19,000
2-Butyl	245 *	13,750	—	—
2-But-*cis*-2′-enyl	242	13,250	—	—
2-But-*trans*-2′-enyl	242 *	9,700	269 *	18,900
2-But-2′-ynyl	239	11,050	—	—
2-Pentyl	245 *	13,350	267 *	31,250
2-Penta-*cis*-2′ : 4′-dienyl	231	17,200	232, 268	25,350, 27,500
2-Penta-*trans*-2′ : 4′-dienyl	225 *	31,200	226,* 271 *	31,250, 26,000
2-Pent-4′-en-2′-ynyl	226, 234	17,900, 18,600	236, 268	18,300, 23,250

* Absorptions thus marked were determined with a Hilger Uvispek Photoelectric Spectrophotometer H700, and the remainder with a Unicam Photoelectric Spectrophotometer SP.500.

The following ketones were prepared similarly (for light absorptions see the Table):

*3-Methyl-2-propyl*cyclo*hex-2-enone* (from propyl bromide) (40% overall), b. p. 100—101°/10 mm., n_D^{20} 1·4871 (Found: C, 77·9; H, 10·25. $C_{10}H_{16}O$ requires C, 78·9; H, 10·6%) [*semicarbazone*, plates (from aqueous ethanol), m. p. 179—180·5° (Found: C, 62·7; H, 9·05. $C_{11}H_{19}ON_3$ requires C, 63·1; H, 9·15%)].

2-Allyl-3-methyl*cyclo*hex-2-enone (5 g.) was reduced in methanol over palladised barium sulphate to an uptake of 1 mol. hydrogen. Filtration and distillation gave 3-methyl-2-propyl-*cyclo*hex-2-enone (4·1 g., 81%), b. p. 108—110°/18 mm., n_D^{20} 1·4860 (semicarbazone, m. p. and mixed m. p. 179—180°).

*2-Butyl-3-methyl*cyclo*hex-2-enone* (57%), regenerated from the semicarbazone with aqueous oxalic acid,[10] had a bitter-sweet odour, b. p. 63°/0·1 mm., n_D^{20} 1·4875 (Found: C, 79·2; H, 11·0. $C_{11}H_{18}O$ requires C, 79·5; H, 10·9%). The *semicarbazone* separated as plates, m. p. 154·5—155·5°, from aqueous ethanol or ethyl acetate (Found: C, 64·7; H, 9·9. $C_{12}H_{21}ON_3$ requires

[10] Harper, *J.*, 1946, 892.

C, 64·5; H, 9·5%), and the 2 : 4-*dinitrophenylhydrazone* as red needles, m. p. 144°, from ethanol (Found: C, 58·2; H, 6·1. $C_{17}H_{22}O_4N_4$ requires C, 58·9; H, 6·4%).

2-*But*-cis-2′-*enyl*-3-*methyl*cyclo*hex*-2-*enone* (60%), b. p. 78—79°/0·2 mm., n_D^{20} 1·5070 (Found: C, 79·9; H, 9·85. $C_{11}H_{16}O$ requires C, 80·4; H, 9·85%). The *semicarbazone* crystallised from ethanol, m. p. 175—176° (Found: C, 65·3; H, 8·55. $C_{12}H_{19}ON_3$ requires C, 65·2; H, 8·65%), and the 2 : 4-*dinitrophenylhydrazone* as red laths, m. p. 147—149° (Found: C, 59·3; H, 5·8. $C_{17}H_{20}O_4N_4$ requires C, 59·3; H, 5·85%).

Ethyl 3-oxo-oct-6-enoate [6] (4·6 g.) was added to a cold, stirred solution of sodium (0·6 g.) in ethanol (15 ml.). After 30 min. the mixture was cooled to 0° and 4-diethylaminobutan-2-one methiodide [5] (7·0 g.) added in ethanol (15 ml.) during 30 min., then the whole was kept for 1 hr. at room temperature and refluxed for 3 hr. Next day the solvent was distilled off, the product isolated with ether and heated under reflux with 10% ethanolic potassium hydroxide (20 ml.) during 7 hr., and the solution then evaporated. The residue was acidified with dilute hydrochloric acid and heated at 50° for 1 hr. The decarboxylated product was isolated with ether and distilled, to give 2-but-*cis*-2′-enyl-3-methyl*cyclo*hex-2-enone (1·5 g., 37%), b. p. 79—80°/0·3 mm., n_D^{20} 1·5030, max. at 240 mμ (ε 11,300). The semicarbazone had m. p. and mixed m. p. 171—175° and the 2 : 4-dinitrophenylhydrazone m. p. and mixed m. p. 147—149°.

2-*But*-trans-2′-*enyl*-3-*methyl*cyclo*hex*-2-*enone* (45%) had a spicy odour, b. p. 72—75°/0·3 mm., n_D^{20} 1·5063 (Found: C, 80·0; H, 9·8. $C_{11}H_{16}O$ requires C, 80·5; H, 9·8%). The *semicarbazone* separated as needles (from ethyl acetate), m. p. 173—175° after softening at 168° (Found: C, 64·8; H, 8·7. $C_{12}H_{19}ON_3$ requires C, 65·1; H, 8·65%).

2-*But*-2′-*ynyl*-3-*methyl*cyclo*hex*-2-*enone* (from but-2-ynyl chloride [6]) (30% overall), b. p. 98—100°/0·3 mm., n_D^{20} 1·5186 (Found: C, 79·8; H, 8·7. $C_{11}H_{14}O$ requires C, 81·4; H, 8·7%) [*semicarbazone* (from ethanol), m. p. 222—223° (Found: C, 65·4; H, 7·45. $C_{12}H_{17}ON_3$ requires C, 65·7; H, 7·8%)].

3-*Methyl*-2-*pentyl*cyclo*hex*-2-*enone* (54% from undistilled keto-ester), regenerated from the semicarbazone,[18] had b. p. 125°/11 mm., n_D^{20} 1·4857 (Found: C, 79·5; H, 11·4. $C_{12}H_{20}O$ requires C, 80·0; H, 11·4%). The *semicarbazone* formed plates, m. p. 149—150·5°, from aqueous ethanol (Found: C, 65·8; H, 9·7. $C_{13}H_{23}ON_3$ requires C, 65·8; H, 9·8%), and the 2 : 4-*dinitrophenylhydrazone* red plates, m. p. 109°, from ethanol (Found: C, 59·8; H, 6·7; N, 14·9. $C_{18}H_{24}O_4N_4$ requires C, 60·0; H, 6·7; N, 15·5%).

3-*Methyl*-2-*pent*-trans-2′-*enyl*cyclo*hex*-2-*enone* (from pent-*trans*-2-enyl bromide [7]) (54% overall), b. p. 90—91°/0·1 mm., n_D^{20} 1·5020 (Found: C, 80·4; H, 10·3. $C_{12}H_{18}O$ requires C, 80·8; H, 10·2%). The *semicarbazone* separated as needles (from aqueous ethanol), m. p. 159·5—161·5° (Found: C, 66·45; H, 8·8. $C_{13}H_{21}ON_3$ requires C, 66·3; H, 9·0%), and the 2 : 4-*dinitrophenylhydrazone* as red needles (from ethanol), m. p. 118° (Found: C, 60·8; H, 6·1. $C_{18}H_{22}O_4N_4$ requires C, 60·3; H, 6·2%).

3-*Methyl*-2-(*penta*-trans-2 : 4-*dienyl*)cyclo*hex*-2-*enone* (from penta-*trans*-2 : 4-dienyl chloride,[9] b. p. 74—76°/175 mm., n_D^{20} 1·4920) (44% overall), b. p. 95—97°/0·25 mm., n_D^{20} 1·5372 (Found: C, 81·3; H, 9·5. $C_{12}H_{16}O$ requires C, 81·8; H, 9·2%). The *semicarbazone* formed yellow prisms, m. p. 143·5—145·5°, from aqueous ethanol (Found: C, 66·6; H, 8·3. $C_{13}H_{19}ON_3$ requires C, 66·9; H, 8·3%). The maleic anhydride adduct separated from benzene, during 10 days at room temperature, as needles, m. p. 130—165°. Crystallisation from ethyl acetate raised the m. p. to 168—178° but did not sharpen it.

3-*Methyl*-2-(*pent*-trans-2-*en*-4-*ynyl*)cyclo*hex*-2-*enone* (40% from undistilled keto-ester), b. p. 85—86°/0·05 mm., 108—112°/0·2 mm., n_D^{20} 1·5408 (Found: C, 81·5; H, 8·1. $C_{12}H_{14}O$ requires C, 82·7; H, 8·1%). The *semicarbazone* separated as yellow prisms, m. p. 164—167° (decomp.), from aqueous ethanol (Found: C, 66·9; H, 7·3. $C_{13}H_{17}ON_3$ requires C, 67·5; H, 7·4%), and the 2 : 4-*dinitrophenylhydrazone* as red needles (from ethanol), m. p. 145·5—146·5° (Found: C, 60·6; H, 4·9. $C_{18}H_{16}O_4N_4$ requires C, 61·0; H, 5·1%).

3-*Methyl*-2-(*pent*-4-*en*-2-*ynyl*)cyclo*hex*-2-*enone* (from pent-4-en-2-ynyl chloride [8]) (15% overall), b. p. 100—101°/0·2 mm., n_D^{20} 1·5354 (Found: C, 80·5; H, 8·35. $C_{12}H_{14}O$ requires C, 82·7; H, 8·1%) [*semicarbazone* (from ethanol), m. p. 203·5—204·5° (Found: C, 67·4; H, 7·35. $C_{13}H_{17}ON_3$ requires C, 67·5; H, 7·4%)].

The above ketones, particularly the acetylenic ketones, generally gave low analyses for carbon. The analogous *cyclo*pentenones behaved similarly.[18]

Selective Hydrogenation of 3-*Methyl*-2-(*pent*-4-*en*-2-*ynyl*)cyclo*hex*-2-*enone*.—This ketone (550

mg.) was shaken in ethyl acetate (15 ml.) with lead-poisoned palladised calcium carbonate [19] (100 mg.) and quinoline (250 mg.) under hydrogen to an uptake of 0·96 mol. Filtration and fractional distillation gave impure 3-*methyl*-2-(*penta*-cis-2 : 4-*dienyl*)cyclo*hex*-2-*enone* (250 mg., 46%), b. p. 95—96°/0·1 mm., n_D^{20} 1·5196 (Found : C, 79·7; H, 9·1. $C_{12}H_{16}O$ requires C, 81·8; H, 9·15%), for light absorption see the Table. Prepared in pyridine–ethanol, the semicarbazone separated as an oil, but on cold storage in ethanol a few crystals separated and on recrystallisation had m. p. 168—170°, after softening at 155°, for light absorption see the Table. The 2 : 4-*dinitrophenylhydrazone*, after passage through activated alumina in benzene and crystallisation from aqueous ethanol, had m. p. 118—120° [Found (on 1·3 mg.) : C, 58·4; H, 5·9. $C_{18}H_{20}O_4N_4$ requires C, 60·6; H, 5·7%].

Selective Hydrogenation of 3-*Methyl*-2-(*pent*-trans-2-*en*-4-*ynyl*)cyclo*hex*-2-*enone*.—This ketone (1·84 g.) was shaken in ethyl acetate with palladised calcium carbonate (not Lindlar) (50 mg.) under hydrogen to an uptake of 1·0 mol. Filtration and fractional distillation at 0·05 mm., gave fractions (i) b. p. 64—67° (0·52 g.), n_D^{20} 1·514, (ii) b. p. 73—74° (0·65 g.), n_D^{20} 1·528, and (iii) b. p. 74—77° (0·35 g.), n_D^{20} 1·535. Fraction (ii) was converted into the semicarbazone and recrystallised from aqueous ethanol, forming yellow prisms, m. p. 143·5—145°, max. at 232, 271 mμ (ε 19,300, 24,000) (Found : C, 66·35; H, 8·3. Calc. for $C_{13}H_{19}ON_3$: C, 66·9; H, 8·3%). Regeneration of the ketone from the semicarbazone (250 mg.) with oxalic acid [18] and fractional distillation gave impure 3-methyl-2-(penta-*trans*-2 : 4-dienyl)*cyclo*hex-2-enone (50 mg.), b. p. 77°/0·05 mm., n_D^{20} 1·520, max. at 232 mμ (ε 15,850) (Found : C, 79·5; H, 10·0. Calc. for $C_{12}H_{16}O$: C, 81·8; H, 9·2%). The 2 : 4-*dinitrophenylhydrazone* separated as red needles (from ethanol), m. p. 126° after softening at 117° (Found : C, 59·8; H, 5·7. $C_{18}H_{20}O_4N_4$ requires C, 60·7; H, 5·6%).

Selective Hydrogenation of Pent-trans-2-*en*-4-*ynol*.—This alcohol [20] (9·4 g.) was shaken in ethyl acetate with palladised calcium carbonate (0·5 g.) under hydrogen to an uptake of 0·95 mol. After filtration and evaporation the product was fractionally distilled. Fractions (5·1 g.) having b. p. 52—55°/12 mm., n_D^{20} 1·475—1·486, were converted into penta-*trans*-2 : 4-dienyl chloride [9] (3·0 g.), b. p. 70—72°/170 mm., n_D^{20} 1·488, and thence (cf. p. 1086) into impure 3-methyl-2-(penta-*trans*-2 : 4-dienyl)*cyclo*hex-2-enone (2·34 g.), b. p. 98—103°/0·2 mm., n_D^{20} 1·536. The semicarbazone separated as yellow prisms (from 2-ethoxyethanol), whose m. p. 136—146° did not sharpen on recrystallisation, max. at 231, 270 mμ (ε 25,700, 20,400) (Found : C, 66·9; H, 8·3. Calc. for $C_{13}H_{19}ON_3$: C, 66·9; H, 8·2%).

4-*Bromo*-3 : 5 : 5-*trimethyl*cyclo*hex*-2-*enone*.—*iso*Phorone (13·8 g., 0·1 mol.) and freshly recrystallised *N*-bromosuccinimide (17·8 g., 0·1 mol.) were heated under reflux in carbon tetrachloride (30 ml.). Reaction commenced after 10 min. and was complete in a further 20 min. The ice-cooled suspension was filtered from succinimide (9·7 g., 98%), and the solvent removed at 30° by a water-pump. The residue (21 g.) was dissolved in light petroleum (20 ml.; b. p. 60—80°) and kept at 0°. Next day the crystals were collected and recrystallised from light petroleum, to give 4-*bromo*-3 : 5 : 5-*trimethyl*cyclo*hex*-2-*enone* (10·8 g., 50%), m. p. 48—49·5° (Found : C, 49·8; H, 5·9; Br, 36·5. $C_9H_{13}OBr$ requires C, 49·8; H, 6·0; Br, 36·8%). The bromo-ketone distilled without decomposition (b. p. 70°/0·1 mm.) and resolidified. If the whole product was distilled before crystallisation appreciable decomposition occurred.

4-*Acetoxy*-3 : 5 : 5-*trimethyl*cyclo*hex*-2-*enone*.—The crystalline bromo-ketone (19·6 g., 0·09 mol.) and dry silver acetate (20 g., 0·12 mol.) were stirred in glacial acetic acid (80 ml.) at 90° during 3 hr. The cooled suspension was filtered from silver bromide (19·5 g., 90%), the filtrate concentrated under reduced pressure, and the product taken into ether, washed, dried ($MgSO_4$), and distilled, to give 4-*acetoxy*-3 : 5 : 5-*trimethyl*cyclo*hex*-2-*enone* (5·5 g., 31%), b. p. 92—95°/0·5 mm., n_D^{20} 1·5128, max. at 229 mμ (ε 9650) (Found : C, 68·9; H, 8·35. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%). The 2 : 4-*dinitrophenylhydrazone*, crystallised from ethanol, had m. p. 152·5—154° (Found : C, 54·8; H, 5·45. $C_{17}H_{20}O_6N_4$ requires C, 54·2; H, 5·4%).

4-(±)-trans-*Chrysanthemoyloxy*-3 : 5 : 5-*trimethyl*cyclo*hex*-2-*enone*.—The crystalline bromo-ketone (1·0 g.) and silver (±)-*trans*-chrysanthemate [12] (1·2 g.) were heated under reflux in xylene during 30 min. [no reaction occurred in benzene, light petroleum (b. p. 60—80°), or carbon tetrachloride]. Filtration and distillation gave the *ester* (0·8 g., 56%), b. p. 132—133°/0·1 mm., n_D^{20} 1·5005, max. at 210 mμ (ε 13,800) (Found : C, 75·3; H, 9·55. $C_{19}H_{28}O_3$ requires C, 75·0; H, 9·25%).

[19] Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446.
[20] Haynes, Heilbron, Jones, and Sondheimer, *J.*, 1947, 1583.

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Hydrolysis of 4-*Bromo*-3 : 5 : 5-*trimethyl*cyclo*hex*-2-*enone*.—The crystalline bromo-ketone (5·4 g.) was stirred in aqueous sodium carbonate (5·3 g. in 50 ml.) at room temperature for 12 hr. and then at 50° for 4 hr. After cooling, the neutral product was extracted with ether, washed with 5% sodium hydroxide, dried, and distilled, to give impure 4-*hydroxy*-3 : 5 : 5-*trimethyl*cyclo*hex*-2-*enone* (1·5 g., 39%), b. p. 68—70°/0·1 mm., n_D^{20} 1·5170, max. at 225 mμ (ε 9050) (Found : C, 73·7; H, 9·1. $C_9H_{14}O_2$ requires C, 70·1; H, 9·15%). Acidification of the sodium hydroxide washings and crystallisation of the solid from light petroleum (b. p. 60—80°) gave 3 : 4 : 5-trimethylphenol, m. p. 106—107°, max. at 206, 279 mμ (ε 18,700, 2200) (Found : C, 79·3; H, 8·75. Calc. for $C_9H_{12}O$: C, 79·4; H, 8·9%). The literature [21] gives m. p. 106° for 3 : 4 : 5-trimethylphenol; no other trimethylphenol has a m. p. above 100°. 3 : 4 : 5-*Trimethylphenyl* 3 : 5-*dinitrobenzoate* separated from light petroleum (b. p. 60—80°) as needles, m. p. 195° (Found : C, 58·0; H, 4·3. $C_{16}H_{14}O_6N_2$ requires C, 58·2; H, 4·3%). Esterification of 3 : 4 : 5-trimethylphenol (0·8 g.) with (±)-*trans*-chrysanthemoyl chloride [1] (1·0 g.) in pyridine–benzene gave 3 : 4 : 5-*trimethylphenyl* (±)-trans-*chrysanthemate* (1·2 g., 75%), prisms (from methanol), m. p. 66—67·5°, max. at 210 mμ (ε 25,000) (Found : C, 79·8; H, 9·35. $C_{19}H_{26}O_2$ requires C, 79·9; H, 9·15%).

Hydrolysis of 4-*Acetoxy*-3 : 5 : 5-*trimethyl*cyclo*hex*-2-*enone*.—The acetoxy-ketone (2·5 g.) was dissolved in 1 : 1 aqueous-methanolic potassium hydroxide (0·7 g. in 20 ml.) and left at room temperature during 50 hr. After evaporation the product was isolated with ether and distilled (0·8 g.; b. p. 70—72°/0·1 mm., n_D^{20} 1·519). The 3 : 5-dinitrobenzoate, prepared in the usual manner from this oil, had m. p. and mixed m. p. 195—196°, when admixed with 3 : 4 : 5-trimethylphenyl 3 : 5-dinitrobenzoate.

Ethyl 3-*Allyl*-4-*methyl*-2-*oxo*cyclo*hex*-2-*enecarboxylate*.—2-Allyl-3-methyl*cyclo*hex-2-enone (5·5 g.) in dry ether (5 ml.) was added during 20 min. to a stirred, gently boiling suspension of sodium hydride (1·92 g.) in ethyl carbonate (9·5 g.) and ether (20 ml.) under nitrogen. After a further 4 hr. moist ether was added and the suspension poured on ice (50 g.) and glacial acetic acid (6·5 g.). The oil was taken up in more ether, washed with sodium hydrogen carbonate, dried, and fractionally distilled. The *ester* produced (4·20 g., 52%) had b. p. 115—116°/0·05 mm., n_D^{20} 1·5022 (Found : C, 70·25; H, 8·55. $C_{13}H_{18}O_3$ requires C, 70·2; H, 8·2%), and gave a deep purple ferric colour.

Ethyl 3-*Allyl*-1-*chloro*-4-*methyl*-2-*oxo*cyclo*hex*-2-*enecarboxylate*.—The above keto-ester (11·5 g.) was added dropwise to a suspension of powdered sodium (1·15 g.) under ether (30 ml.). Next day toluene-*p*-sulphonyl chloride (9·5 g.) in ether (30 ml.) was added, causing a heavy white precipitate. After 1 hour's refluxing water was added to dissolve the solid, and the organic product extracted with ether. The extracts were washed with sodium hydrogen carbonate, dried, and fractionally distilled. Solid separated from the higher-boiling fractions but the desired *ethyl* 3-*allyl*-1-*chloro*-4-*methyl*-2-*oxo*cyclo*hex*-2-*enecarboxylate* (1·25 g.) was obtained as a liquid, b. p. 104—105°/0·05 mm., n_D^{20} 1·500 (Found : C, 61·7; H, 7·0; Cl, 13·3. $C_{13}H_{17}O_3Cl$ requires C, 60·8; H, 6·7; Cl, 13·8%).

The experimental work described in this paper was carried out during 1948—1950 and 1953—1955. A. J. B. E. is indebted to the Department of Scientific and Industrial Research for a Maintenance Award, and M. A. K. to the Government of Sind for an Overseas Scholarship. We thank Miss J. A. Hutchinson for the (Unicam) ultraviolet light absorption measurements, Dr. R. J. D. Smith for the infrared measurement, and Dr. M. Elliott, Miss J. Kane, and Dr. E. A. Parkin for the insecticidal tests.

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[21] Beilstein, " Handbuch der organischen Chemie," 4th Edn., E II 6, p. 480.

214. iso*Cyanates. Part III.* Benzoyl* iso*Cyanate.*

By C. L. Arcus and B. S. Prydal.

Addition reactions of benzoyl *iso*cyanate are reported which indicate this compound to be among the most reactive of *iso*cyanates.

4-Benzoyl-1-phenyl- and 4-benzoyl-1-*p*-nitrophenyl-semicarbazide, derived from benzoyl *iso*cyanate, have been cyclised to 3-hydroxy-1 : 5-diphenyl- and -1-*p*-nitrophenyl-5-phenyl-1 : 2 : 4-triazole.

In connection with an investigation of the Hofmann reaction with *C*-benzoylformamide (Part II) it was observed that benzoyl *iso*cyanate undergoes vigorous hydrolysis with aqueous alkali, yielding benzamide. Billeter [1] found benzoyl *iso*cyanate to react with ammonia, aniline, benzamide, benzenesulphonamide, and ethanol to yield, respectively, benzoyl-, *N*-benzoyl-*N'*-phenyl-, dibenzoyl-, and *N*-benzenesulphonyl-*N'*-benzoyl-urea, and ethyl benzoylcarbamate; with urea it yields 1-benzoylbiuret.[2] Benzoyl *iso*cyanate appeared, therefore, to be a markedly reactive *iso*cyanate, and further reactions of this compound, together with its use in ring-closure, have been investigated.

Benzyl, *iso*propyl, *tert.*-butyl, and 1-methyl-1-α-naphthylpropyl benzoylcarbamate, Ph·CO·NH·CO·OR, have been prepared by the reaction of the corresponding alcohol with benzoyl *iso*cyanate. Since difficulty is, in some instances, experienced in the preparation of urethanes from tertiary alcohols, it is noteworthy that satisfactory derivatives were obtained from the two tertiary alcohols above.

From benzylamine there was obtained *N*-benzoyl-*N'*-benzylurea, Ph·CO·NH·CO·NH·CH_2Ph. Both the NH_2-groups of hydrazine reacted with benzoyl *iso*cyanate, yielding 1 : 2-bisbenzoylcarbamoylhydrazine, (Ph·CO·NH·CO·NH)$_2$. The arylhydrazines Ar·NH·NH_2 [Ar = Ph, *p*-C_6H_4·NO_2, 2 : 4-$C_6H_3(NO_2)_2$] yielded the corresponding 1-aryl-4-benzoylsemicarbazides, Ar·NH·NH·CO·NH·COPh. (Phenylhydrazine reacts with phenyl *iso*cyanate to yield 1 : 4-diphenylsemicarbazide,[3] whence it is known that the NH_2 rather than the NHPh group reacts with an *iso*cyanate).

The presence of an electron-attracting (−*I*, −*M*) *p*-nitro-group in *p*-nitrophenyl *iso*cyanate has been found by Baker and Holdsworth [4] to increase the rate of reaction with methanol by a factor of 130 (under the stated conditions) in comparison with that of phenyl *iso*cyanate. Attempts were made to compare the rates of reaction of *p*-nitrophenyl and benzoyl *iso*cyanate with the same alcohol, by devising conditions under which both urethanes, but neither *iso*cyanate, could be precipitated and collected, but no

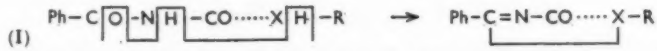
satisfactory procedure was found. However, it is considered, in view of the reactions which it undergoes, that benzoyl *iso*cyanate is among the most reactive of *iso*cyanates; this is ascribed to (*a*) inductive electron-attraction by the carbonyl and phenyl constituents of the benzoyl group adjacent to the *iso*cyanate group, and (*b*) conjugation of the lone-pair on the nitrogen atom with the benzoyl-carbonyl group; both effects render the carbon atom of the *iso*cyanate group exceptionally prone to attack by an electron-donor. In each of the reactions above the donor is either $-\ddot{O}-$ or $>\ddot{N}-$.

Derivatives of benzoyl *iso*cyanate of type (I), in which either one or two atoms separate

* Part II, *J.*, 1954, 4018.

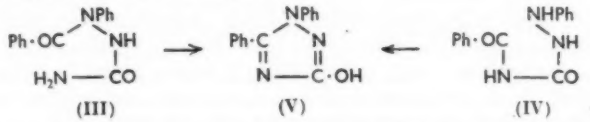
[1] Billeter, *Ber.*, 1903, **36**, 3218.
[2] Hill and Degnan, *J. Amer. Chem. Soc.*, 1940, **62**, 1595.
[3] Freund and Goldsmith, *Ber.*, 1888, **21**, 2464.
[4] Baker and Holdsworth, *J.*, 1947, 716.

XH from the nearest carbonyl group, are potentially convertible, by elimination of the elements of water, into rings of type (II).



From 4-benzoyl-1-phenyl- and -*p*-nitrophenyl-semicarbazide the corresponding ring-compounds have been prepared; it has not been found possible to cyclise the derivatives of benzyl alcohol, benzylamine, and 2 : 4-dinitrophenylhydrazine.

By the action of aqueous sodium hydroxide followed by acidification with acetic acid, Widman [5] cyclised 1-benzoyl-1-phenylsemicarbazide (III). Similar treatment of 4-benzoyl-1-phenylsemicarbazide (IV) has been found to yield the same compound, 3-hydroxy-1 : 5-diphenyl-1 : 2 : 4-triazole (V).



The formation of this from the isomeric compound (IV) provides additional evidence for the structure of the latter; were the compound the isomeric 4-benzoyl-2-phenylsemicarbazide, NH_2·NPh·CO·NH·COPh, then the product would be 5-hydroxy-1 : 3-diphenyl-1 : 2 : 4-triazole. This compound has m. p. 229—230°,[6] whereas (V) has m. p. 288—289°.

The relatively mild procedure above did not effect ring closure of the other semicarbazides. A number of examples of cyclisation by the use of polyphosphoric acid have been reported,[7] and on being heated with this reagent the compound (IV) yielded the triazole (V). On similar treatment 4-benzoyl-1-*p*-nitrophenylsemicarbazide gave 3-hydroxy-1-*p*-nitrophenyl-5-phenyl-1 : 2 : 4-triazole, but 4-benzoyl-1-(2 : 4-dinitrophenyl)semicarbazide was not changed.

Experimental

M. p.s are corrected.

Benzoyl *iso*cyanate was prepared as described in Part II. The reactions below were carried out in a flask fitted with a condenser and, where required, a dropping funnel, to each of which was attached a calcium chloride tube; heating was by an oil-bath; all solvents were dried, and benzoyl *iso*cyanate was exposed as little as possible to moist air.

Reactions with Alcohols.—To benzyl alcohol (1·1 g.) in benzene (5 ml.) was added benzoyl *iso*cyanate (1·5 g.) in benzene (8 ml.); the solution was heated for ½ hr. at 70°, and on cooling yielded *benzyl benzoylcarbamate* (2·4 g.), m. p. 113—114°, which after recrystallisation from aqueous ethanol (1 : 1) had m. p. 115—115·5° (Found: C, 70·3; H, 5·0; N, 5·85. $C_{15}H_{13}O_3N$ requires C, 70·6; H, 5·15; N, 5·5%).

To *iso*propyl alcohol (15 ml.) was added benzoyl *iso*cyanate (1·5 g.); the solution was heated for ¾ hr. at 65°; *isopropyl benzoylcarbamate* (0·9 g.) separated on cooling, and on recrystallisation from benzene formed needles, m. p. 99—100° (Found: C, 63·85; H, 6·45; N, 6·9. $C_{11}H_{13}O_3N$ requires C, 63·75; H, 6·3; N, 6·75%).

To *tert.*-butyl alcohol (30 ml.) was added benzoyl *iso*cyanate (3·0 g.). An immediate reaction occurred; the flask was thereafter heated for 10 min. at 90°. On cooling there separated tert.-*butyl benzoylcarbamate* (2·9 g.), needles, m. p. 146—147°, unchanged by recrystallisation from aqueous ethanol (1 : 1) (Found: C, 65·45; H, 6·9; N, 6·1. $C_{12}H_{15}O_3N$ requires C, 65·15; H, 6·85; N, 6·35%).

To 1-methyl-1-α-naphthylpropanol (2·0 g., m. p. 50°) in ether (10 ml.), benzoyl *iso*cyanate (1·5 g.) in ether (8 ml.) was added; the ether was allowed to evaporate, yielding a product (2·9 g.), m. p. 119—121°, which on recrystallisation from ethanol gave 1-*methyl*-1-α-*naphthylpropyl benzoylcarbamate*, needles, m. p. 122° (decomp.) (Found: C, 75·7; H, 6·15; N, 4·1. $C_{22}H_{21}O_3N$ requires C, 76·05; H, 6·1; N, 4·05%).

[5] Widman, *Ber.*, 1896, **29**, 1951.
[6] Wheeler and Stratiropoulos, *Amer. Chem. J.*, 1905, **34**, 128.
[7] Birch, Jaeger, and Robinson, *J.*, 1945, 585; Koo, *J. Amer. Chem. Soc.*, 1953, **75**, 1891.

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Reactions with Amines.—Reaction of benzylamine (1·1 g.) and benzoyl *iso*cyanate (1·5 g.), as for benzyl alcohol, gave *N*-benzoyl-*N'*-benzylurea (1·95 g.), m. p. 160—162°, which after recrystallisation from ethanol formed needles, m. p. 165—166° (Found: C, 70·65; H, 5·45; N, 11·25. Calc. for $C_{15}H_{14}O_2N_2$: C, 70·85; H, 5·55; N, 11·0%). Wheeler and Johnson [8] record m. p. 165—166°.

To a stirred suspension of hydrazine hydrate (1·0 g.; 100%) in ether (10 ml.) was added benzoyl *iso*cyanate (2·4 g.) in ether (24 ml.). Immediate reaction occurred, and there separated a product (2·5 g.), m. p. 240—241° (decomp.), for which no satisfactory solvent was found. It was heated at 80°/1 mm. in a sublimation apparatus, when a relatively small amount of a lower-melting by-product sublimed; there remained 1 : 2-*bisbenzoylcarbamoylhydrazine*, m. p. 250° (Found: C, 58·6; H, 4·7; N, 17·2. $C_{16}H_{14}O_4N_4$ requires C, 58·95; H, 4·3; N, 17·15%).

To phenylhydrazine (3·9 g.) in benzene (20 ml.) was added benzoyl *iso*cyanate (5·9 g.) in benzene (20 ml.); the solution was heated for 10 min. at 70°; on cooling there separated 4-*benzoyl*-1-*phenylsemicarbazide* (7·2 g.), needles, m. p. 191—192°, which after recrystallisation from methanol had m. p. 194—195° (Found: C, 66·15; H, 5·05; N, 16·4. $C_{14}H_{13}O_2N_3$ requires C, 65·8; H, 5·15; N, 16·45%).

To *p*-nitrophenylhydrazine (6·0 g.) in dioxan (100 ml.), benzoyl *iso*cyanate (6·0 g.) in dioxan (30 ml.) was added; the solution was heated for ½ hr. at 70°. On cooling there separated 4-*benzoyl*-1-p-*nitrophenylsemicarbazide* (10·1 g.), m. p. 224—226·5°, which on recrystallisation from 2-ethoxyethanol formed yellow needles, m. p. 226—227° (Found: C, 56·1; H, 3·95; N, 18·35. $C_{14}H_{12}O_4N_4$ requires C, 56·0; H, 4·05; N, 18·65%).

Similar interaction of 2 : 4-dinitrophenylhydrazine (8·0 g.) in dioxan (125 ml.) and benzoyl *iso*cyanate (6·0 g.) in dioxan (30 ml.) gave a product (10·6 g.), m. p. 204—205°, which after recrystallisation from 2-ethoxyethanol yielded 4-*benzoyl*-1-(2 : 4-*dinitrophenyl*)*semicarbazide*, yellow needles, m. p. 210·5—211·5° (Found: C, 48·9; H, 3·25; N, 19·95. $C_{14}H_{11}O_6N_5$ requires C, 48·7; H, 3·2; N, 20·3%).

Ring-closure.—4-Benzoyl-1-phenylsemicarbazide (4·2 g.) was dissolved in 10% aqueous sodium hydroxide (63 ml.) at 50°, and the solution was poured into aqueous acetic acid (50%; 70 ml.). The product (2·5 g.) was heated with ethanol (175 ml.), and the solution filtered; the filtrate yielded 3-hydroxy-1 : 5-diphenyl-1 : 2 : 4-triazole (1·6 g.), m. p. 288—289°, unaltered by further recrystallisation (Found: C, 70·35, 70·1; H, 4·5, 4·6; N, 17·3. Calc. for $C_{14}H_{11}ON_3$: C, 70·65; H, 5·0; N, 17·65%). Recorded m. p.s: 288—290°.[5, 9]

To 4-benzoyl-1-phenylsemicarbazide (0·5 g.) was added polyphosphoric acid (5 g.; P_2O_5 content, 83%); the mixture was heated at 65° for ½ hr., a clear solution being obtained. It was poured into ice-water; there immediately separated 3-hydroxy-1 : 5-diphenyl-1 : 2 : 4-triazole (0·35 g.), having m. p. 285—287° and, after recrystallisation from ethanol, m. p. 288—289° alone and when mixed with the above specimen.

Similar reaction of 4-benzoyl-1-*p*-nitrophenylsemicarbazide (1·1 g.) with polyphosphoric acid (10 g.), but at 105° for 1 hr., yielded 3-*hydroxy*-1-p-*nitrophenyl*-5-*phenyl*-1 : 2 : 4-*triazole* (1·1 g.), m. p. 263—265°, which on recrystallisation from chlorobenzene formed yellow needles, m. p. 265—266° (Found: C, 59·6; H, 3·9; N, 19·5. $C_{14}H_{10}O_3N_4$ requires C, 59·55; H, 3·55; N, 19·85%).

Similar treatment did not cyclise 4-benzoyl-1-(2 : 4-dinitrophenyl)semicarbazide, which was recovered.

Thanks are expressed to the Government Grants Committee of the Royal Society and to Imperial Chemical Industries Limited for grants.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, October 24th*, 1956.]

[8] Wheeler and Johnson, *Amer. Chem. J.*, 1902, **27**, 218.
[9] Young, *J.*, 1895, **67**, 1064.

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215. *Red-seaweed Polysaccharides. Part II.** Porphyra capensis *and the Separation of* D- *and* L-*Galactose by Crystallisation.*

By J. R. Nunn and (Mrs.) M. M. von Holdt.

A polysaccharide, isolated from the red seaweed *Porphyra capensis*, was found to consist of D- and L-galactose, 6-*O*-methyl-D-galactose, 3 : 6-anhydro-L-galactose, and a hydrogen sulphate in the approximate molecular ratio 1 : 1 : 2 : 1. D- and L-Galactose were separated by recrystallisation.

The polysaccharides of the *Porphyra* species of the Rhodophyceae have received little attention and only in the case of *P. umbilicalis*,[2] which yielded a mannan on extraction with sodium hydroxide solution, has any detailed investigation been made. Apart from this there have been reports of the isolation of DL-galactose from *P. laciniata*,[3] *P. tenera*,[3] and *P. crispata*,[4] and of galactose, glucose, pentose, and methylpentose from *P. tenera*.[5]

Several of the *Porphyra* species are extensively used as human foods in various parts of the world, especially in the Far East, and the " laver bread " of Wales is chiefly made from *P. umbilicalis*. Their value as a food presumably lies in their high protein content, which (by nitrogen estimation) lies between 25 and 30% on a dry weight basis.

P. capensis, which grows in profusion on the Atlantic side of the Cape Peninsula and along several other parts of the South African coast, afforded a sulphated polysaccharide, as its mixed sodium–magnesium salt, in about 30% yield by extraction with hot water. The polysaccharide was hydrolysed and chromatography of the neutralised hydrolysate revealed the presence of two sugars, namely, galactose and another almost coincident on paper with fucose. This mixture was separated on a cellulose column, and the second sugar proved to be 6-*O*-methyl-D-galactose by oxidation of the sugar with periodate: this sugar gave 4 mol. of formic acid and consumed 4 mol. of periodate, and methoxyacetaldehyde was isolated from the reaction mixture. As additional evidence 6-*O*-methyl-D-galactose was synthesised for comparison by methylation of 1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose with Purdie's reagents, followed by acid hydrolysis. This is the first recorded instance of 6-*O*-methyl-D-galactose in Nature.

Crystallisation of the galactose fraction from methanol yielded L-galactose, which required a large number of recrystallisations before it had a constant melting point. A part of the mother-liquor from the first crystallisation afforded 2-DL-galactobenziminazole when treated according to Moore and Link's procedure, indicating the presence of D-galactose [6] in the solution. Concentration of the remainder of the mother-liquor afforded another crop of crystals, which had a positive rotation. Repeated recrystallisation of this product from methanol afforded pure D-galactose. The separation of D- and L-galactose from synthetic mixtures containing an excess of the L-enantiomorph was repeated several times, and although it appears to be the first recorded separation by crystallisation of a pair of enantiomorphs in the sugar series, it is by no means unique as other separations, such as that of D- and L-threonine,[7] are on record.

Methanolysis of the polysaccharide and separation of the products on a cellulose column afforded, in the first fraction, methyl 3 : 6-anhydro-α-L-galactopyranoside, indicating that 3 : 6-anhydro-L-galactose also occurred in the polysaccharide. The

* Part I, *J.*, 1957, 197. A preliminary note on Part II has appeared.[1]

[1] Nunn and von Holdt, *Chem. and Ind.*, 1956, 467.
[2] Jones, *J.*, 1950, 3292.
[3] Oshima and Tollens, *Ber.*, 1901, **34**, 1422.
[4] Hayashi, *J. Soc. Trop. Agr.* (*Taihoku Imp. Univ.*), 1941, **13**, 193.
[5] Hibino, *J. Chem. Soc. Japan*, 1942, **63**, 1078.
[6] Bell and Baldwin, *J.*, 1941, 125.
[7] Velluz and Amiard, *Bull. Soc. chim. France*, 1953, 903.

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following fraction contained more 3 : 6-anhydro-α-L-galactopyranoside, but it was contaminated with the methyl glycosides of galactose and 6-*O*-methyl-D-galactose, and no attempt was made to separate the mixture.

3 : 6-Anhydro-sugars are extremely labile and are not amenable to the ordinary methods of sugar analysis. One method has been published [8] but it gave unsatisfactory results in our hands, and we have been unable to obtain direct evidence for the amount of 3 : 6-anhydro-sugar in the polysaccharide. However, if it is assumed that the polysaccharide consists only of the above three sugars and ester sulphate it appears, from analyses of galactose, 6-*O*-methyl-D-galactose, and sulphate on the purified sodium salt of the polysaccharide, that the molecular ratio of galactose : 6-*O*-methyl-D-galactose : 3 : 6-anhydro-L-galactose : sulphate is approximately 1 : 1 : 2 : 1. Such a repeating unit would have an equivalent weight (for the sodium salt) of 729 (Found : 740). The methoxyl content of such a repeating unit should be 4·2% (Found : 5·6%); this discrepancy could possibly be accounted for by adsorbed ethanol on the polysaccharide, which is often difficult to remove from polysaccharides prepared by precipitation in ethanol.[9]

Experimental

Unless otherwise stated, concentration of solutions was carried out at 40°/20 mm. and specific rotations were measured in H_2O. Paper chromatograms were run in (*a*) ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4), (*b*) butanol–pyridine–water (9 : 2 : 2), or (*c*) butanol–ethanol–water (40 : 11 : 19). M. p. are corrected.

Isolation and Purification of the Polysaccharide.—Extraction was carried out on fresh material owing to the difficulty experienced in extracting material previously dried at 45°. Fresh (wet) *Porphyra capensis* (5·5 kg., *i.e.*, *ca.* 0·5 kg. dry wt.) was mixed with water and acetic acid added to pH 2. The acid caused rapid disintegration of the weed and did not appear to degrade the polysaccharide. Steam was passed into the mixture for ½ hr. after disintegration of the weed had begun. The pH rose to between 6 and 7 during this operation. The extract was strained through a wire sieve and then introduced into a continuous centrifuge (23,000 r.p.m.) while still hot, yielding a clear pale brown liquid. A colloidal precipitate, which appeared on cooling, was separated by passing the mixture through a continuous centrifuge at 50,000 r.p.m. Precipitation into ethanol (5 vols.) and washing with ethanol and acetone afforded a white product (164 g., *ca.* 32% on a dry wt. basis) [Found (on material dried at 60°/0·5 mm.) : N, 1·6; SO_4^{2-} (after hydrolysis), 13·0; ash (carbonated), 15·5%]. Analysis of the ash indicated the presence of iron (trace), magnesium, and sodium. Attempts to remove the protein [10] by shaking a solution with chloroform were ineffective. The polysaccharide was further purified for analysis by passing a solution through Amberlite IR-120 and IRA-400 resins. The acid eluate was exactly neutralised with sodium hydroxide solution, and the polysaccharide precipitated in excess of ethanol. The precipitate was collected in a centrifuge, washed with ethanol, and dried, then having $[\alpha]_D^{18}$ −60° [Found (on material dried at 60°/0·5 mm.) : N, 0·2; OMe, 5·6; SO_4^{2-} (after hydrolysis), 12·9; ash (sulphated), 12·6%. Equiv. (from SO_4^{2-} detn.), 740]. Galactose and 6-*O*-methylgalactose were estimated in a hydrolysate of the polysaccharide, after separation on a paper chromatogram, with maltose as reference sugar,[11] by Somogyi's micro-method [12] [Found : galactose (calc. as $C_6H_{10}O_5$), 23·1, 23·0; 6-*O*-methyl-D-galactose (calc. as $C_7H_{12}O_5$), 29·4, 30·1%]. The value for 6-*O*-methyl-D-galactose is probably too high since, although 3 : 6-anhydro-L-galactose is largely destroyed during prolonged acid hydrolysis, some might have remained and both sugars run to nearly the same position on a chromatogram.

Hydrolysis of the Polysaccharide.—Hydrolysis of the polysaccharide in N-sulphuric acid for 16 hr. at 100° and chromatography of the neutralised (barium carbonate) hydrolysate revealed the presence of two spots, one of which corresponded in position to galactose. The second spot R_R (relative to rhamnose), 0·79 in (*a*), 0·65 in (*b*), 0·84 in (*c*), almost exactly coincided with fucose, 0·79 in (*a*), 0·70 in (*b*), 0·87 in (*c*). However, the colour of the spot when sprayed with *p*-anisidine hydrochloride was different from that of fucose, especially under ultraviolet light.

[8] Smith, O'Neill, and Perlin, *Canad. J. Chem.*, 1955, **33**, 1353.
[9] Percival and Ross, *J.*, 1950, 717.
[10] Sevag, Smolens, and Lackman, *J. Biol. Chem.*, 1938, **124**, 425.
[11] Flood, Hirst, and Jones, *J.*, 1948, 1679.
[12] Somogyi, *J. Biol. Chem.*, 1952, **195**, 19.

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For the isolation of these sugars the polysaccharide (45 g.) was hydrolysed with N-sulphuric acid (400 c.c.), and the mixture neutralised and evaporated to a syrup (36·6 g.), which was separated on a cellulose column (7·6 × 48 cm.) with butanol–water (9 : 1), giving fractions (1) 8·6 g., and (2) 11·9 g.

6-O-*Methyl*-D-*galactose*.—Fraction (1) was decolorised with charcoal in water, the solution was filtered and evaporated to dryness, and the residue recrystallised from ethanol, yielding colourless needles, m. p. 122—123°, $[\alpha]_D^{17}$ +117° ⟶ + 77·3° in 4·5 hr. (*c* 2·02) (Found: C, 43·2; H, 7·45; OMe, 16·2. Calc. for $C_7H_{14}O_6$: C, 43·3; H, 7·3; OMe, 16·0%). The osazone, recrystallised from methanol, had m. p. 196—197°, $[\alpha]_D^{19}$ +137° (*c* 0·42 in pyridine).

This sugar (*ca.* 10 mg.) was demethylated by 48% hydrobromic acid in a sealed tube in a water-bath for 5 min.[13] The solution was neutralised (Amberlite IR-4B resin) and filtered. Chromatography of the filtrate revealed spots corresponding to galactose and to the original material.

When the above sugar was oxidised in the usual manner with 0·04M-sodium metaperiodate, 3·79 mol. of formic acid per mol. of substance were liberated, and 4·0 mol. of periodate per mol. of substance were consumed. A large-scale oxidation of the sugar (0·5 g.) was effected with sodium metaperiodate (3 g.) in water (5·0 c.c.) for 24 hr. After the addition of N-hydrochloric acid (30 c.c.) and 20% sodium arsenite solution (30 c.c.) to remove the iodine, 8% sodium acetate solution (20 c.c.) and 8% ethanolic dimedone solution (10 c.c.) were added to the mixture, which was heated on a boiling-water bath for 10 min. When cool the crystals were filtered off and recrystallised from aqueous ethanol; they had m. p. and mixed m. p. with the dimedone complex of methoxyacetaldehyde, 169—170°. The latter was prepared by periodate oxidation of glycerol 1-methyl ether.[14]

For the preparation of 6-*O*-methyl-D-galactose, 1 : 2-3 : 4-di*iso*propylidene-D-galactose was methylated with methyl iodide and silver oxide, and, after filtration and evaporation of the filtrate, the residue was hydrolysed with N-sulphuric acid. This solution was neutralised (barium carbonate), filtered, and evaporated, and the residue fractionated on a cellulose column. The fraction containing 6-*O*-methyl-D-galactose, recrystallised from ethanol or methanol, had m. p. and mixed m. p. with the 6-*O*-methyl-D-galactose isolated from the polysaccharide, 122—123°.

The m. p. and optical rotation of 6-*O*-methyl-D-galactose have been recorded as: m. p. 128°, $[\alpha]_{578}^{20}$ +114° ⟶ +77°;[15] m. p. 118°, $[\alpha]_D^{20}$ +120° ⟶ +70°;[16] m. p. 122—123°, $[\alpha]_D^{18}$ +112° ⟶ +66°;[16] m. p. 113—114°, $[\alpha]_D^{18}$ +137° ⟶ +77°;[17] m. p. 119·5—120·5°.[18] Chromatographic fractionation enabled us to prepare a very pure specimen in the present investigation, and it seems possible that some of the earlier preparations were contaminated with other material. 6-*O*-Methyl-D-galactosazone has similarly been recorded on several occasions, as having: m. p. 204—206°, $[\alpha]_{578}^{17}$ +135 in pyridine;[15] m. p. 200—201°, $[\alpha]_D^{20}$ +141° in pyridine;[16] m. p. 200°, $[\alpha]_D^{26}$ +141 ⟶ +92° (after 24 hr., const.) in pyridine;[17] m. p. 201—203°.[19]

D- *and* L-*Galactose*.—Fraction (2) (11·9 g.), when recrystallised several times from methanol, had m. p. and mixed m. p. with authentic L-galatose 161—162°, $[\alpha]_D^{17}$ −83·3° (*c* 1·1). The m. p. was depressed to 155° on admixture with D-galactose. The sugar gave mucic acid, m. p. and mixed m. p. 215—217°, on oxidation with nitric acid (*d* 1·15). The methylphenylhydrazone, crystallised from methanol, had m. p. and mixed m. p. 174°. When this L-galactose was mixed in equimolecular proportions with D-galactose it had zero rotation (*c* 1·6).

The mother-liquor from the first recrystallisation of fraction (2) was used to prepare a benziminazole according to Moore and Link's procedure.[20] The product, on recrystallisation from water, had m. p. 227° and zero rotation in 5% citric acid. Bell and Baldwin [6] report that 2-DL-galactobenziminazole is less soluble than either the D- or the L-form and that it has m. p. 233° and zero rotation in 5% citric acid solution. The mother-liquor from the first recrystallisation of the L-galactose yielded more crystals on concentration. This material had a positive

[13] Hough, Jones, and Wadman, *J.*, 1950, 1702.
[14] Hatch and Nesbitt, *J. Amer. Chem. Soc.*, 1945, **67**, 39.
[15] Freudenberg and Smeykal, *Ber.*, 1926, **59**, 100.
[16] Munro and Percival, *J.*, 1936, 640.
[17] Pacsu and Trister, *J. Amer. Chem. Soc.*, 1940, **62**, 2301.
[18] Hough, Jones, and Magson, *J.*, 1952, 1525.
[19] Dewar and Percival, *J.*, 1947, 1622.
[20] Moore and Link, *J. Biol. Chem.*, 1940, **133**, 293.

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rotation and on repeated recrystallisation from methanol was shown to be D-galactose, m. p. 161—162°, $[\alpha]_D^{18}$ +84° (*c* 0·6). It gave mucic acid, m. p. and mixed m. p. 215—217°, on oxidation with nitric acid (*d* 1·15). It had zero rotation when mixed with an equal weight of the L-isomer. The methylphenylhydrazone had m. p. and mixed m. p. 174—175° with authentic material prepared from D-galactose and it depressed the m. p. (168—171°) of the material prepared from L-galactose.

When a mixture of L-and D-galactose in the ratio of 4 : 1 was recrystallised from methanol, L-galactose, $[\alpha]_D^{18}$ −83° (*c* 0·9), was recovered from the first recrystallisation. Partial evaporation of the mother-liquors afforded D-galactose which, after further recrystallisation, had $[\alpha]_D^{17}$ +90°. The mother-liquor left after the D-galactose had crystallised had $[\alpha]_D^{18}$ +28°. This separation was repeated several times.

Methanolysis of the Polysaccharide.—To the crude polysaccharide (21 g.), dried at 60°/1 mm., was added 2·5% anhydrous methanolic hydrogen chloride (500 c.c.). This was refluxed for 15 hr., neutralised with silver carbonate and the residue removed in a centrifuge. Evaporation of the clear solution afforded a syrup (21 g.), which was mixed with cellulose powder packed on top of a cellulose column (41 × 5·5 cm.), and was eluted with butanol–water (9 : 1). The first fraction (2·87 g.) was a syrup. It gave a positive Molisch reaction and a faint spot R_B 2·2, R_F 0·55, when chromatographed in solvent (*a*) and sprayed with periodate–benzidine [21] or the periodate–starch spray of Metzenberg and Mitchell.[22] On distillation it yielded a main fraction (2·32 g.), b. p. 165—175°/0·1 mm., as a pale yellow oil which partly solidified, $[\alpha]_D^{18}$ −38° (*c* 2·23). The mixture of oil and solid was hydrolysed on a boiling-water bath with 0·1N-acetic acid, and this solution, which restored the colour to Schiff's reagent, was used for the preparation of the phenylosazone, which was obtained as yellow crystals (from methanol), m. p. and mixed m. p. 203—205° with 3 : 6-anhydro-L-galactose phenylosazone. Trituration of the mixture of oil and crystals with ethyl acetate afforded colourless needles, which after recrystallisation from the same solvent, had m. p. and mixed m. p. 138·5—140° with methyl 3 : 6-anhydro-α-L-galactopyranoside, $[\alpha]_D^{19}$ −77° (*c* 0·9).

The 3 : 6-anhydro-L-galactose isolated did not represent the total amount in the methanolysate. The remaining fractions obtained from the cellulose column after the first were contaminated with methyl galactofuranosides and 6-*O*-methylgalactofuranosides, which run very close to it on a chromatogram.

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National Chemical Research Laboratory,
Pretoria, S. Africa. [*Received, September 21st*, 1956.]

[21] Cifonelli and Smith, *Analyt. Chem.*, 1954, **26**, 1132.
[22] Metzenberg and Mitchell, *J. Amer. Chem. Soc.*, 1954, **76**, 4187.

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216. *Chemistry of the Higher Fungi. Part VII.* Odyssic Acid and Odyssin.*

By J. D. Bu'Lock, E. R. H. Jones, and P. R. Leeming.

Odyssic acid and odyssin, which accompany nemotinic acid and nemotin as fungus metabolites, are shown to be 4-hydroxydodeca-5 : 6-diene-8 : 10-diynoic acid (III) and the corresponding lactone (IV), respectively, *i.e.*, C_{12} homologues of the C_{11} compounds, nemotinic acid and nemotin.

The principal acetylenic constituents of the aqueous medium of cultures of the Basidiomycete B.841 are nemotinic acid and nemotin which have the structures (I) and (II), respectively.[1] In describing their purification by counter-current distribution we reported their separation from a pair of closely similar compounds; for these the names odyssic acid and odyssin were proposed. We now report the characterisation of these compounds

* Part VI, Bu'Lock, Jones, Leeming, and Thompson, *J.*, 1956, 3767.

[1] Bu'Lock, Jones, and Leeming, *J.*, 1955, 4270.

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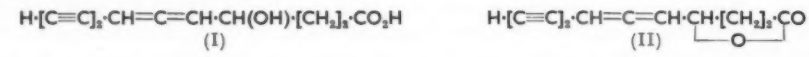
as homologues of the constituents (I) and (II) in which the acetylenic $C_{(11)}$ hydrogen atom is replaced by a methyl group.

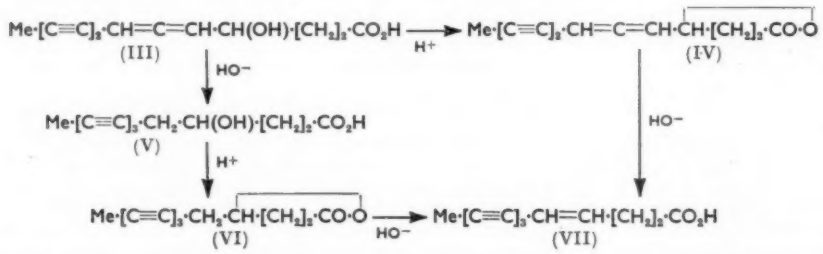


This structural difference presumably underlies our finding that odyssic acid, odyssin, and various derived compounds, although still very difficult to handle, are uniformly more stable than corresponding compounds of the nemotinic acid series already described;[1,2] several compounds were obtained crystalline, and rather more significance could be attached to analytical data than in the earlier work. Nevertheless the techniques used in that work were retained, and, with the reservation that smaller amounts of material were available (particularly of odyssin [1]), the same reactions and interconversions were effected as in the nemotinic acid series, including the alkali-catalysed rearrangements,[2] in one of which the formation of stereoisomers has been observed.

Odyssic acid, obtained from the counter-current distribution of crude nemotinic acid [1] and purified by redistribution in the same solvent system, could be isolated only as a labile gum. Methylation gave a non-crystalline hydroxy-ester. Both are strongly dextrorotatory and give infrared spectra very similar to those of nemotinic acid (I) and its methyl ester, with the important difference that there is no band at 3300 cm.$^{-1}$, *i.e.*, no ≡C—H group. This suggested that odyssic acid was an alkylated derivative of acid (I), a view substantiated by the ultraviolet absorption spectrum, which is very similar to that of acid (I) but with the bathochromic shift of some 20 Å to be expected on alkylation of the enediyne chromophore (cf. Table). Odyssic acid was converted by sulphuric acid–dioxan into a γ-lactone (carbonyl band at 1785 cm.$^{-1}$) which was also a labile gum. This lactone was identical with purified natural odyssin in its infrared and ultraviolet spectra and behaviour with aqueous alkali (see below). The spectroscopic properties of odyssin bear the same relation to those of odyssic acid as do those of nemotin to nemotinic acid.[1]

The rearrangement of nemotinic acid by aqueous alkali was shown in Part VI [2] to give the corresponding non-allenic triyne, *iso*nemotinic acid, in which the asymmetric centre at $C_{(4)}$ remained intact. On the other hand the rearrangement of the γ-lactone nemotin gives an ene-triyne acid, nemotin A, and in this reaction the lactone function disappears. The mechanism of this reaction requires that the lactone function (and therefore the hydroxyl group of the parent acid) should be adjacent to the allene group.

Precisely analogous reactions were established for odyssic acid and odyssin. *iso*-Odyssic acid was obtained as a photosensitive crystalline solid by the alkali treatment of



odyssic acid. The product was characterised as a 4-hydroxy-triynoic acid by conversion into its γ-lactone, a crystalline, optically active compound, polymorphic with m. p.s 64—66°, 73—74°, and 93—98°; this had, as expected, the ultraviolet absorption spectrum of a triyne and, in the infrared spectrum, a carbonyl band at 1796 cm.$^{-1}$ (γ-lactone) but no allene band.

[2] Bu'Lock, Jones, Leeming, and Thompson, *J.*, 1956, 3767.

Alkali-treatment of odyssin gave an acid, odyssin-A, with the ultraviolet absorption spectrum of a dialkyl-enetriyne (cf. Table; compare nemotin-A), and the infrared spectrum of its methyl ester confirms that there is no hydroxyl group, lactone ring, or allene group

Ultraviolet absorption spectra.

Substance	Absorption max. (Å) and log ε (in parentheses)								
Odyssic acid (III)	2110	—	2380	2505	2650	2805			
	(4·78)	—	(3·77)	(4·02)	(4·18)	(4·09)			
Nemotinic acid (I) [1]	2090	—	2375	2495	2635	2785			
	(4·65)	—	(3·75)	(4·02)	(4·19)	(4·09)			
Odyssin (IV) (natural and from odyssic acid)	2100	—	2375	2500	2640	2800			
	(4·78)	—	(3·75)	(4·03)	(4·20)	(4·10)			
Nemotin (II) [1]	2085	—	2365	2490	2625	2780			
	(4·76)	—	(3·79)	(4·03)	(4·19)	(4·09)	—	—	—
*iso*Odyssic lactone (VI)	2095	—	2400	2530	2680	2860	3085		
	(5·21)	—	(2·18)	(2·32)	(2·43)	(2·40)	(2·19)		
*iso*Nemotinic lactone [2]	2060	—	2400	2530	2680	2850	3040		
	(5·11)	—	(2·16)	(2·28)	(2·42)	(2·41)	(2·20)		
Odyssin-A (VII) (from odyssin and from *iso*odyssic lactone)	2100	2240	2310	2425	2580	2730	2895	3085	3300
	(4·71)	(4·53)	(4·86)	(5·08)	(3·54)	(3·85)	(4·13)	(4·26)	(4·09)
Nemotin-A [2]	2115	2230 *	2300	2410	2580	2720	2885	3070	3280
	(4·37)	(4·47)	(4·77)	(4·93)	(3·44)	(3·78)	(4·07)	(4·19)	(4·04)
trans-Odyssin-A methyl ester...	—	2240	2310	2430	2585	2735	2900	3090	3310
		(4·44)	(4·82)	(5·05)	(3·56)	(3·87)	(4·14)	(4·25)	(4·10)
Nemotin-A methyl ester [2]	2120	2230 *	2300	2410	2570	2720	2880	3070	3280
	—	—	—	—	—	—	—	—	—

* Inflexion.

in the molecule. Material obtained by esterification of the total isomerisation product did not melt sharply and its infrared spectrum showed bands at both 950 (*trans*-C=C) and 740 cm.$^{-1}$ (*cis*-C=C), also present before esterification. However, the acid could be purified by crystallisation, and methylation of the crystallised acid gave an ester, m. p. 61·5—64·5°, which showed only the absorption band at 950 cm.$^{-1}$ and is therefore the *trans*-isomer; * methylation of material from the mother-liquors gave a concentrate of the *cis*-form. From infrared spectra of the mixed reaction products it may be concluded that isomerisation of odyssin gives about 75% of the *trans*-isomer, and re-examination of the infrared data for the whole product of the nemotin–nemotin-A isomerisation [2] indicates that this reaction too gives a mixture containing an appreciable proportion of the *cis*-isomer.

As with nemotin-A, odyssin-A could also be obtained, in rather poor yield (<20%), by alkali treatment of the lactone from *iso*odyssic acid. The product was only characterised by its ultraviolet absorption spectrum, but in the similar reaction of *iso*nemotinic lactone,[2] re-examination of our infrared data again reveals that a mixture of *cis*- and *trans*-nemotin-A was produced.

These observations established the structure of the skeleton of odyssic acid as $C_n{\cdot}[C{\equiv}C]_2{\cdot}CH{=}C{=}CH{\cdot}CH(OH){\cdot}C{\cdot}C{\cdot}CO_2H$ and the chain length was settled by the hydrogenation of odyssin-A. The acid produced was converted directly into its *p*-toluidide, which depressed the m. p. of undecano- and tridecano-*p*-toluidides but not that of dodecano-*p*-toluidide.

Hence odyssic acid and odyssin are, respectively, 4-hydroxydodeca-5 : 6-diene-8 : 10-diynoic acid (III) and the corresponding lactone (IV), the C_{12} homologues of the C_{11} compounds, nemotinic acid and nemotin. *iso*Odyssic acid is (V), its lactone (VI), and odyssin-A is (VII). The ultraviolet absorption spectra of these compounds are summarised in the Table; comparison with the data for corresponding compounds of the C_{11} series

* The structure and configuration assigned to *trans*-odyssin-A have now been confirmed by comparison of its methyl ester with synthetic methyl *trans*-dodec-4-ene-6 : 8 : 10-triynoate (Jones, Skatteböl, and Whiting, unpublished work).

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shows in each case the bathochromic shift of *ca.* 15—20 Å due to alkylation of the chromophore.

It is unusual in studies of natural products to encounter a compound occurring together with a *C*-methyl derivative. In the present instance there are at least three possible biogenetic explanations. Odyssic acid might be formed by a route similar to, but largely independent of, the biosynthesis of the lower homologue. Or both compounds might be formed from a single closely-related precursor, for example in a scheme such as:

$$\text{(reduction) } R{\cdot}CH_3 \longleftarrow R{\cdot}CO_2H \longrightarrow R{\cdot}H \text{ (decarboxylation)}$$

A third possibility is the direct transfer of a methyl group as such from an "active methyl" donor to nemotinic acid. Studies on this and other aspects of the biosynthesis are in progress; meanwhile it may be observed that the present instance of the co-occurrence of C_{11} and C_{12} compounds emphasises the fact that, though many natural acetylene derivatives belong in a formal sense to the series of unsaturated fatty acids, the polyacetylenes in general do not show that preponderance of even-numbered carbon chains so characteristic of the natural fats.

Experimental

The general experimental techniques were similar to those outlined in earlier papers.[1,2]

Odyssic Acid (III).—The acid was separated from nemotinic acid by counter-current distribution as described previously [1] and purified by redistribution in the same benzene–water system (60 transfers in 40 tubes). Spectroscopic assay indicated a yield of purified odyssic acid of *ca.* 30 mg./l. of culture medium; the acid had $[\alpha]_D^{20}$ +300° (*c*, 0·25); pK_a (in water) 4·90; ultraviolet absorption, cf. Table; infrared absorption, bands at 3520 and 3600 (O—H), 2300—3500 (CO·O—H), 2230 (C≡C), 1960 (C=C=C), and 1710 cm.$^{-1}$ (HO·C=O); no band at 3300 cm.$^{-1}$ (no ≡C—H). Evaporation of solutions of the acid gave a labile gum. Esterification with diazomethane gave methyl odyssate, a labile oil; ultraviolet absorption, cf. Table; infrared absorption bands at 1740 (MeO·C=O) and 3470 and 3620 cm.$^{-1}$ (O—H).

Odyssin (IV).—Separated from nemotin as previously described [1] and purified by redistribution in the same system (*n*-heptane–aqueous ethanol), natural odyssin (*ca.* 80% pure) was obtained only in small amounts (*ca.* 5 mg./l. of culture-medium on spectroscopic assay) and identified by comparison of its infrared spectrum with that of the lactone from odyssic acid (see below); $[\alpha]_D^{20}$ +360° (*c*, 0·2); ultraviolet absorption spectrum (qualitative only), cf. Table.

Odyssin from Odyssic Acid.—A solution of the acid (300 mg.) in pure dry dioxan (300 c.c.) was treated with sulphuric acid (9 c.c.), and the solution left for 4 days in the dark at 20°, after which water (50 c.c.) was added followed by sodium hydrogen carbonate solution to bring the solution to pH 4. Sodium sulphate was filtered off and washed with ether, and the combined filtrate and washings evaporated to 80 c.c. Water (3·5 l.) was added and the solution extracted with ether (2 × 350 c.c.). The combined extracts, when washed with water (2 × 200 c.c.) and dried, contained *ca.* 160 mg. of neutral polyacetylenes. Of this 100 mg. were purified by counter-current distribution between 32% aqueous ethanol and *cyclo*hexane. The purified odyssin (76 mg.) was a labile oil; $[\alpha]_D^{20}$ +345° (*c*, 0·24); ultraviolet absorption, cf. Table; infrared absorption identical with natural odyssin, with band at 1785 cm.$^{-1}$ (γ-lactone).

iso*Odyssic Acid* (V).—A solution of odyssic acid (100 mg.) in ether was shaken with 0·1N-sodium hydroxide (2 × 100 c.c.) and the combined aqueous extracts were kept for 2 hr. at 20°, the ultraviolet absorption spectrum then showing no further change; a small amount of enetriyne had been formed. The solution was acidified and extracted with ether (2 × 150 c.c.), and the extracts combined, dried, and evaporated. The residue of *iso*odyssic acid, recrystallised from ether–pentane at −40°, formed persistently yellow needles, m. p. 128—130°, still containing some enetriyne as shown by the ultraviolet absorption spectrum. The compound was therefore purified by counter-current distribution between ether and M/15-disodium hydrogen phosphate solution, and the purified material converted into its lactone (see below).

iso*Odyssic Lactone* (VI).—A solution of *iso*odyssic acid (80 mg.) and sulphuric acid (3 c.c.) in pure dry dioxan (100 c.c.) was kept in the dark at 20° for 4 days. The solution was then neutralised with sodium hydrogen carbonate solution and the precipitated sodium sulphate filtered off

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and washed with ether. The combined filtrate and washings were evaporated to 30 c.c. and poured into water (800 c.c.); the solution was extracted with ether (2 × 200 c.c.), and the ether extracts washed with water (3 × 200 c.c.), dried, and concentrated to 100 c.c. The pale yellow solution was decolorised with a little charcoal, evaporated, and iso*odyssic lactone* crystallised from methylene chloride–pentane forming trimorphic plates, m. p.s 64°, 73—74°, and 93—98°, stable for several days at −40° in the dark (Found: C, 76·9; H, 5·5. $C_{12}H_{10}O_2$ requires C, 77·4; H, 5·4%); $[\alpha]_D^{20}$ −2° (*c*, 0·5); ultraviolet absorption, cf. Table; infrared absorption with band at 1795 cm.$^{-1}$ (γ-lactone) and no allene band.

Odyssin-A from Odyssin.—Odyssin (from odyssic acid) (180 mg.) in ether (450 c.c.) was added to 0·1N-sodium hydroxide (500 c.c.), and the ether evaporated; after 2 hr. the solution was acidified and extracted with ether (2 × 300 c.c.). The yellow extracts were added to M/15-disodium hydrogen phosphate (300 c.c.), the ether was evaporated, and the aqueous solution then extracted with ether (5 × 300 c.c.), giving a colourless solution (methylation of the dissolved material and measurement of the infrared spectrum of the product showed this to be a mixture of *cis*- and *trans*-isomers). Evaporation of the solution and recrystallisation of the residue from methylene chloride–pentane at −80° gave trans-*odyssin-A* (yield *ca.* 60%) as rhombs, becoming slowly yellow in light, decomp. at 185—195° (Found: C, 77·2; H, 5·7%; equiv., 179. $C_{12}H_{10}O_2$ requires C, 77·4; H, 5·4%; equiv., 186); ultraviolet absorption, cf. Table; infrared absorption, band at 1710 cm.$^{-1}$ (HO·C=O), no allene or hydroxyl bands.

Methyl Esters of Odyssin-A.—Methylation with distilled diazomethane of the total reaction product (above) gave material which did not melt sharply and had infrared absorption bands at 740 (*cis*-CH=CH) and 950 cm.$^{-1}$ (*trans*-CH=CH). Methylation of recrystallised odyssin-A in the same way gave methyl *trans*-odyssin-A, which crystallised from *n*-pentane at −70° as needles, m. p. 61·5—64·5°, mixed m. p. 59·5—62·5° with synthetic material (cf. footnote, p. 1099) (m. p. 57·5—61·5°), ultraviolet (cf. Table) and infrared absorption identical with synthetic material, the latter showing bands at 1740 (MeO·C=O) and 950 cm.$^{-1}$ (*trans*-CH=CH) and no allene, hydroxyl, or *cis*-CH=CH bands. Similar methylation of material from the liquors remaining after crystallisation of *trans*-odyssin-A gave an oil, shown by its infrared absorption spectrum to contain *ca.* 60% of methyl *cis*-odyssin-A and *ca.* 40% of the *trans*-ester.

Odyssin-A from iso*Odyssic Lactone.*—The lactone (6 mg.) in dioxan (13 c.c.) and 10% aq. potassium carbonate (13 c.c.) was left at 20°; the ultraviolet absorption spectrum (cf. Table) indicated a fairly rapid reaction affording about 20% of odyssin-A.

Hydrogenation of Odyssin-A.—The acid (45 mg.) in ethanol (25 c.c.) over platinum (from 50 mg. of oxide) rapidly took up 6·9 mol. of hydrogen; filtration and evaporation of the solution gave *n*-dodecanoic acid (50 mg.) identified by conversion into the *p*-toluidide, m. p. 84—85°, and comparison with authentic material. Mixed m. p. with dodecano-*p*-toluidide (m. p. 85·5—86·5°), 84—86°, with undecano-*p*-toluidide (m. p. 78·5—79·5°), 76·5—78·5°, with tridecano-*p*-toluidide (m. p. 88·0—88·5°) 81—84°.

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217. *7-Hydroxy-3 : 6-ditiglyloxytropane, a New Alkaloid isolated from the Roots of* Datura.

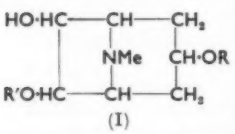
By W. C. Evans and M. W. Partridge.

A hitherto unknown alkaloid, shown by hydrolysis to be a ditiglyl ester of 3 : 6 : 7-trihydroxytropane, has been isolated from the roots of three species of *Datura*. The formation of 6 : 7-dihydroxy-3-tiglyloxytropane (meteloidine) by partial hydrolysis establishes the constitution of the new base as 7-hydroxy-3 : 6-ditiglyloxytropane.

Members of the genus *Datura* have long been known to contain in their aerial parts alkaloids of the tropane group, notably hyoscyamine, hyoscine, and meteloidine. Little is known of the alkaloids occurring in the roots of these plants, except for mention of hyoscyamine in *D. stramonium* L.[1] and *D. tatula* L.[2]

The crude mixture of bases resulting from extraction of the basified, powdered root with ether furnished an apparently homogeneous base as a colourless gum on fractional elution from a phosphate buffer–kieselguhr column. The base afforded an optically inactive, crystalline hydrobromide of molecular formula, $C_{18}H_{27}O_5N,HBr$, a picrate $C_{18}H_{27}O_5N,C_6H_3O_7N_3$, and a chloroplatinate $(C_{18}H_{27}O_5N)_2,H_2PtCl_6$. In the roots of *D. stramonium* L. and *D. tatula* L. var. *inermis*, this alkaloid formed about 10% of the total alkaloids present, whereas in *D. ferox* L. it accounted for 30% of the total basic constituents.

Evidence for its structure was obtained by hydrolysis. On being heated with aqueous-ethanolic barium hydroxide, it underwent complete hydrolysis and furnished 3 : 6 : 7-trihydroxytropane (teloidine) (I; R = R′ = H) and tiglic acid. The yield of the acid indicated that the parent compound was a ditiglyl ester of teloidine. The formation of 6 : 7-dihydroxy-3-tiglyloxytropane (meteloidine) (I; R = CH_3·CH:CMe·CO, R′ = H) on partial hydrolysis by aqueous barium hydroxide served to orientate the position of both ester groups. The new alkaloid is clearly (±)-7-hydroxy-3 : 6-ditiglyloxytropane (I; R = R′ = CH_3·CH:CMe·CO). Confirmation of this structure is provided by its ultraviolet absorption: meteloidine and the new alkaloid both exhibit maxima at 217 mμ (ε 12,200 and 23,900, respectively). Methyl tiglate is reported by Dreiding and Pratt[3] to have $\lambda_{max.}$ 214 mμ (ε 11,300).



(I)

Experimental

Extraction of the Alkaloid.—(i) The powdered root (1 kg.) was moistened with water (500 ml.), kept overnight, mixed with calcium hydroxide (100 g.), and exhaustively extracted by percolation with ether. After removal of the solvent, the dark green residue was stirred with aqueous-ethanolic hydrochloric acid; non-basic material was removed with chloroform, and the bases were liberated by ammonia and collected in chloroform. The crude mixture was transferred to a column prepared from kieselguhr (50 g.) and 0·5M-phosphate buffer (pH 6·6; 50 ml.); the first fraction eluted with light petroleum (b. p. 60—80°) was shown by paper chromatography[4] to be homogeneous and was recovered as a colourless gum. The yields obtained were: *D. ferox* L., 0·05; *D. tatula* L. var. *inermis*, 0·01; *D. stramonium* L., 0·01%.

(ii) For large-scale extractions, the root was percolated with ether as described in the foregoing experiment, the whole process being followed by paper chromatography. The initial fractions of the percolate, which were richest in materials of highest R_F value, were combined

[1] Feldhaus, *Arch. Pharm.*, 1905, **243**, 328.
[2] Klein, "Handbuch der Pflanzenanalyse," Springer, Vienna, 1933, Vol. IV, p. 768.
[3] Dreiding and Pratt, *J. Amer. Chem. Soc.*, 1954, **76**, 1902.
[4] Evans and Partridge, *J. Pharm. Pharmacol.*, 1954, **6**, 702.

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and concentrated. Basic material was collected in 3N-sulphuric acid supported on a column of kieselguhr and, after removal of non-basic material from the column by irrigation with ether, the bases were liberated by irrigation with ammoniacal chloroform. The recovered basic material was neutralised to pH 4 with 0·1N-sulphuric acid, fractionally liberated with 0·1N-sodium hydroxide, and collected in chloroform. The first few fractions, which were shown to be homogeneous by paper chromatography, afforded a colourless gum (0·05 g./kg. of root) on evaporation of the solvent.

Salts.—An ethanolic solution of the base on the addition of aqueous hydrobromic acid gave a *hydrobromide* which crystallised from ethanol as aggregated prisms, $\alpha = 0°$, m. p. 215—216° (Found: C, 51·4; H, 6·6; N, 3·3. $C_{18}H_{27}O_5N,HBr$ requires C, 51·7; H, 6·7; N, 3·35%), $\lambda_{max.}$ in H_2O, 217 mμ (ε 23,900). The *picrate*, prepared by interaction of the hydrobromide and sodium picrate, crystallised from aqueous ethanol as plates, m. p. 184—185° (Found: C, 50·7, 51·0; H, 5·3, 5·1; N, 9·7, 10·0. $C_{18}H_{27}O_5N,C_6H_3O_7N_3$ requires C, 50·9; H, 5·3; N, 9·9%). A neutral solution, prepared by dissolving the gum in dilute hydrochloric acid, furnished with chloroplatinic acid a *chloroplatinate* as orange rosettes which crystallised from very dilute hydrochloric acid as prisms, m. p. 252—253° (decomp.) [Found: C, 40·1; H, 5·6; N, 2·7, 2·4; Pt, 18·0, 18·0. $(C_{18}H_{27}O_5N)_2,H_2PtCl_6$ requires C, 39·9; H, 5·2; N, 2·6; Pt, 18·0%]. An attempt to prepare an oxalate gave partially hydrated prisms, m. p. 128—130° (decomp.).

Hydrolysis.—(i) The alkaloid hydrobromide (0·1 g.), dissolved in ethanol (2 ml.) and mixed with a solution of barium hydroxide (0·5 g.) in water (15 ml.), was heated at 100° in a sealed tube for 2½ hr. Barium was removed from the solution as its carbonate. The filtrate, after being thoroughly washed with ether, gave a crystalline solid on removal of the solvent under reduced pressure. Acetone-soluble material was extracted from this and crystallised from aqueous ethanol as aggregated prisms, m. p. 297—298° (decomp.), undepressed on admixture with teloidine hydrobromide prepared by hydrolysis of meteloidine [Pyman and Reynolds [5] give m. p. 295° (decomp.)]. A second portion of the filtrate when treated with aqueous sodium picrate yielded teloidine picrate which crystallised from aqueous ethanol as needles, m. p. 221—222° (decomp.), undepressed by teloidine picrate derived from meteloidine. Schöpf and Arnold [6] describe teloidine picrate as needles, m. p. 218—219° (decomp.). A third portion of the filtrate gave, with aqueous ammonium reineckate, *teloidine reineckate* which separated from aqueous acetone as leaflets m. p. 195—196° (decomp.); mixed m. p. with a sample of the reineckate obtained from the hydrolysis products of meteloidine, 196—197° (decomp.) {Found: C, 29·4; H, 4·2. $C_9H_{15}O_3N,H[Cr(SCN)_4(NH_3)_2]$ requires C, 29·3; H, 4·5%}.

(ii) The hydrobromide (0·064 g.) was hydrolysed as described in the foregoing experiment. After acidification with hydrobromic acid, ether removed from the solution tiglic acid (0·026 g., 85%), m. p. and mixed m. p. 63·5° (Found: C, 59·8; H, 7·8. Calc. for $C_5H_8O_2$: C, 60·0; H, 8·0%).

(iii) The suspension obtained when the hydrobromide (0·1 g.) was added to barium hydroxide (0·5 g.) in water (10 ml.) was heated with stirring at 100° for 90 min. and kept overnight. The clear, supernatant liquid was extracted with chloroform and, after being concentrated, this solution furnished meteloidine which crystallised as rosettes of needles, m. p. and mixed m. p. 138—139°. When mixed with meteloidine, it behaved as a homogeneous substance on paper chromatography. Its picrate crystallised from aqueous ethanol as nodules, m. p. 177—178°; mixed m. p. with meteloidine picrate 177° (Pyman and Reynolds [5] give m. p. 177—180°). The *reineckate* crystallised from aqueous acetone as plates which collapsed to a viscous mass at 140° and then decomposed slowly both alone and after mixing with meteloidine reineckate {Found: C, 35·3; H, 4·9. $C_{13}H_{21}O_4N,H[Cr(SCN)_4(NH_3)_2]$ requires C, 35·5; H, 4·9%}.

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[*Received, October* 31*st*, 1956.]

[5] Pyman and Reynolds, *J.*, 1908, **93**, 2077.
[6] Schöpf and Arnold, *Annalen*, 1947, **558**, 109.

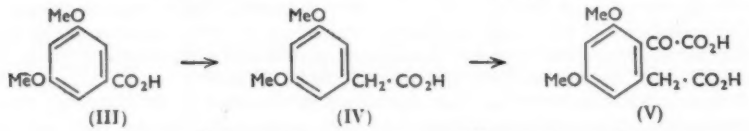
218. *Curvularin. Part II.* The Constitution of an Aromatic Degradation Product and the Partial Structure of Curvularin.*

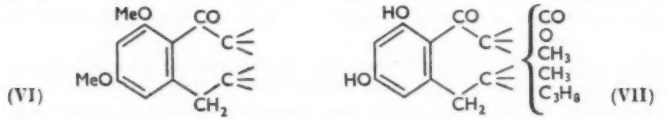
By O. C. Musgrave.

Alkaline hydrolysis of *OO*-dimethylcurvularin followed by permanganate oxidation gives oxalic and succinic acid, and 2-carboxymethyl-4 : 6-dimethoxyphenylglyoxylic acid, the structure of which is confirmed by synthesis. Curvularin is shown to have the partial structure (VII) in which the neighbouring carbonyl group is not coplanar with the benzene ring.

It was shown in Part I * that the mould metabolic product curvularin contains a dihydroxybenzoyl system in which the two hydroxyl groups are *ortho* or *meta* to one another. To orient this group it was desirable to obtain a degradation product containing it intact. Mild alkaline hydrolysis of curvularin gave an acidic material but no homogeneous product could be isolated. Fusion with potassium hydroxide and oxidation with alkaline permanganate solution gave intractable products. *OO*-Dimethylcurvularin, in which the aromatic ring might be expected to be less sensitive than that in curvularin, is insoluble in water, so it was first hydrolysed with alkali and then oxidised in the cold with aqueous potassium permanganate: oxalic and succinic acid and an acid $C_{12}H_{12}O_7$, m. p. 212—212·5°, were isolated by crystallisation. The last-named compound is dibasic, has two methoxyl groups, and therefore contains the aromatic nucleus of *OO*-dimethylcurvularin. In curvularin itself two hydrogen atoms are attached directly to the benzene ring and these are presumably still present in the $C_{12}H_{12}O_7$ acid which accordingly may be written as (I).

$(MeO)_2C_6H_2\{C_2H_2O\}(CO_2H)_2$ (I) $\qquad$ $2:4\text{-}(MeO)_2C_6H_2\cdot CO\{(CH_2)(CO_2H)_2\}$ (II)





The ultraviolet absorption of the acid resembles that of 2 : 4-dimethoxyacetophenone (for these and other $\lambda_{max.}$ and ε see the Table) suggesting that it contains the 2 : 4-dimethoxybenzoyl chromophore. The infrared absorption of the acid is compatible with this, three strong bands being at 1704, 1667, and 1597 cm.$^{-1}$ The first of these is attributed to the carboxylic acid groups (aliphatic acids [1] absorb at *ca.* 1715 cm.$^{-1}$, phenylacetic acid [2] at 1697 cm.$^{-1}$). The second corresponds to the carbonyl group conjugated with the aromatic nucleus, and the third to the conjugated system of such an aromatic ketone. 2 : 4-Dimethoxyacetophenone itself gives strong bands at 1645 (aromatic carbonyl) and 1580 cm.$^{-1}$ (conjugated aromatic system). The displacement of the carbonyl band in the $C_{12}H_{12}O_7$ acid suggests that the group is closely associated with one or both of the carboxylic acid groups (see below). The expression (I) for the $C_{12}H_{12}O_7$ acid may therefore be expanded to (II). Of the compounds having this partial structure only 2-carboxymethyl-4 : 6-dimethoxyphenylglyoxylic acid (V) appears to be compatible

* Part I, *J.*, 1956, 4301.

[1] Grove and Willis, *J.*, 1951, 877.
[2] Flett, *ibid.*, p. 962.

with the chemical and spectral evidence. The formulation as a substituted phenylglyoxylic acid is supported by the resemblance (*a*) of its ultraviolet spectrum to those of 2 : 4-dimethoxy- and 2 : 4-dimethoxy-6-methyl-phenylglyoxylic acid, and (*b*) of its infrared spectrum in the 6 μ region to that of 2 : 4-dimethoxyphenylglyoxylic acid [strong bands at 1715 (carboxylic acid), 1656 (aromatic carbonyl), and 1608 cm.$^{-1}$ (conjugated aromatic system)].

The structure of the $C_{12}H_{12}O_7$ acid was confirmed by synthesis. 3 : 5-Dimethoxybenzoic acid (III) was converted into the acid chloride which by the Arndt–Eistert synthesis [3] gave 3 : 5-dimethoxyphenylacetic acid (IV). The derived methyl ester with ethoxalyl chloride in the presence of anhydrous aluminium chloride [4,5] afforded 2-carboxymethyl-4 : 6-dimethoxyphenylglyoxylic acid, identical (mixed m. p. and infrared spectrum) with the $C_{12}H_{12}O_7$ acid obtained by degradation. [As very few instances [6] of the Friedel–Crafts acylation of esters of phenylacetic acids had been reported it was desirable to ascertain that the reaction would take the normal course. The easily

*Ultraviolet absorption spectra (in ethanol).**

	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε
$C_{12}H_{12}O_7$ acid	2300	11,800	2750	8500	3075	6750
2 : 4-Dimethoxyacetophenone	2275	9500	2695	9550	3050	5650
2 : 4-Dimethoxyphenylglyoxylic acid	2295	11,300	2725	10,800	3095	7800
2 : 4-Dimethoxy-6-methylphenylglyoxylic acid [a] †	*ca.* 2300	9350	2870	10,000	3160	7850
2-Carboxymethyl-4 : 5-dimethoxyphenylglyoxylic acid	2310	19,300	2790	10,200	3065	6450
3 : 4-Dimethoxyacetophenone	2280	16,100	2725	10,600	3035	7550
OO-Dimethylcurvularin	2230	10,500	2675	5100	(2910)	(3600)
2 : 4-Dimethoxy-6-methylacetophenone	2215	10,200	2675	6130	(2920)	(3530)
2-Acetoxyacetophenone	2390	9000	2840	1200	—	—
2-Methylacetophenone [b]	2420	8700	2810	1200	(3310)	(50)
	2450	8300				
4-Acetoxyacetophenone	2480	14,000	—	—	—	—
4-Methylacetophenone [b]	2520	15,100	—	—	—	—
2 : 4-Diacetoxyacetophenone	2480	13,500 [c]	(2830)	(1550)	—	—
2 : 4-Dimethylacetophenone [b]	2510	14,100	2820	1700	—	—
	(2560)	(12,300)	2910	1300		
2 : 4 : 6-Triacetoxyacetophenone [c]	2390	6500	—	—	—	—
2 : 4 : 6-Trimethylacetophenone [d,] ‡	(2390)	(2600)	—	—	—	—
Curvularin diacetate	(2350)	(5600)	—	—	—	—
2 : 4-Dihydroxy-6-methylacetophenone	(2335)	(7600)	2825	9750	3200	6000
2 : 4-Dihydroxyacetophenone	2310	9150	2770	15,300	3145	7900
Curvularin	(2290)	(10,150)	2720	6350	3045	5100

[a] Cram, *J. Amer. Chem. Soc.*, 1950, **72**, 1028. [b] Braude and Sondheimer, *J.*, 1955, 3754. [c] Barton and Bruun, *J.*, 1953, 603. [d] Schwartzman and Corson, *J. Amer. Chem. Soc.*, 1954, **76**, 781.

* Values in parentheses are those of inflections. † In 1 : 1 ethanol–0·1N-hydrochloric acid.

‡ In *cyclo*hexane.

accessible isomeric ester, methyl 3 : 4-dimethoxyphenylacetate, was readily converted into the expected 2-carboxymethyl-4 : 5-dimethoxyphenylglyoxylic acid, the structure of which follows from its analysis and the resemblance of its ultraviolet spectrum to that of 3 : 4-dimethoxyacetophenone.]

The isolation of 2-carboxymethyl-4 : 6-dimethoxyphenylglyoxylic acid from the degradation of *OO*-dimethylcurvularin implies that the latter contains the arrangement (VI), and the two compounds therefore appear to possess the same ultraviolet-light absorbing system. The absorption intensities of *OO*-dimethylcurvularin are, however, much lower than those of the acid. Such a decrease without significant displacement of the maxima frequently indicates considerable non-planarity in the light-absorbing system

[3] Cf. Bachmann and Struve, *Organic Reactions*, 1942, **1**, 38.
[4] Kindler, Metzendorf, and Dschi-yin-Kwok, *Ber.*, 1943, **76**, *B*, 308.
[5] Cf. Sprenger, Ruoff, and Frazer, *J. Amer. Chem. Soc.*, 1950, **72**, 2874.
[6] *E.g.*, Kunckell, *Ber.*, 1905, **38**, 2609.

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caused by the steric requirements of the attached groups.[7] Scale diagrams in which the values for the interference radii suggested by Braude and Sondheimer [7] were used reveal that the hindrance to planarity of the 2 : 4-dimethoxybenzoyl chromophore in the $C_{12}H_{12}O_7$ acid is weak, because of the relatively small steric requirements of the glyoxylic carboxyl group, and is comparable with that in 2 : 4-dimethoxyacetophenone. When the glyoxylic carboxyl group is replaced by the more bulky methyl group, as in 2 : 4-dimethoxy-6-methylacetophenone, steric interference is much increased; the carbonyl group is forced out of the plane of the aromatic ring and, in agreement, this compound shows considerably lower absorption intensities than does its less-hindered analogue 2 : 4-dimethoxyacetophenone. The ultraviolet spectrum of *OO*-dimethylcurvularin bears a very close resemblance to that of the above highly hindered ketone and it is concluded that in this case also the carbonyl group and the aromatic ring are not coplanar. The distortion of the light-absorbing system with consequent reduction in the degree of conjugation is reflected in the high infrared frequency (1695 cm.$^{-1}$) for this carbonyl group, similar to that (1681 cm.$^{-1}$) of 2 : 4-dimethoxy-6-methylacetophenone but much higher than that (1645 cm.$^{-1}$) of 2 : 4-dimethoxyacetophenone.

The ultraviolet spectrum of curvularin diacetate may also be accounted for on this basis. The effects of acetoxyl groups on the absorption of acetophenone are observed to resemble closely those of methyl groups. Thus the spectra of 2- and 4-mono-, 2 : 4-di-, and 2 : 4 : 6-tri-acetoxyacetophenone are similar to those of the corresponding mono-, di-, and tri-methylacetophenones. Curvularin diacetate possesses a spectrum comparable with those of the highly sterically hindered 2 : 4 : 6-triacetoxy- and 2 : 4 : 6-trimethylacetophenone.

While the ultraviolet spectra of *OO*-dimethylcurvularin and 2 : 4-dimethoxy-6-methylacetophenone closely resemble each other, considerable differences in intensities are observed for the corresponding phenols. The absorption of 2 : 4-dihydroxy-6-methylacetophenone is generally similar to that of 2 : 4-dihydroxyacetophenone. This is attributed to the reduction in the degree of distortion of the conjugated system in the highly hindered ketone brought about by hydrogen-bonding between the carbonyl and the *o*-hydroxyl group. In the case of curvularin, hydrogen-bonding is apparently not sufficient to reduce this distortion appreciably. The lower degree of conjugation in curvularin is also seen in its high infrared carbonyl frequency (1653 cm.$^{-1}$) compared with those of 2 : 4-dihydroxy-6-methylacetophenone (1631 cm.$^{-1}$) and 2 : 4-dihydroxyacetophenone (1621 cm.$^{-1}$). It may be concluded that the lack of planarity of the conjugated system in curvularin is caused by large or rigid substituent groups.

Curvularin has been shown previously to contain, in addition to a dihydroxybenzoyl system, a second carbonyl group and two *C*-methyl groups. As *OO*-dimethylcurvularin has now been proved to contain the arrangement (VI), curvularin may be assigned the partial structure (VII) in which the carbonyl group is not coplanar with the aromatic nucleus. The isolation of succinic acid from the oxidation of *OO*-dimethylcurvularin implies that the group $\vdots C \cdot CH_2 \cdot CH_2 \cdot C \vdots$ is present in the latter and also, presumably, in curvularin itself.

Experimental

Analyses are by the microanalytical laboratory of this Department; molecular weights were determined ebullioscopically in acetone. Ultraviolet absorption spectra were determined with a Hilger "Uvispek" spectrophotometer. Infrared absorption spectra were determined, for thin films (of liquids) or Nujol mulls, with a double-beam spectrophotometer with rock-salt optics; the concentrations and thickness of the mulls were not measured.

Hydrolysis and Oxidation of OO-*Dimethylcurvularin.*—*OO*-Dimethylcurvularin (8·9 g.) was heated under reflux in an atmosphere of nitrogen for 1 hr. with sodium hydroxide (4·0 g.) in methanol (50 ml.) and water (50 ml.). Water (50 ml.) was then added and the methanol

[7] Braude and Sondheimer, *J.*, 1955, 3754.

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removed by distillation. A solution of potassium permanganate (54 g.) in water (1100 ml.) was added slowly to the aqueous solution with stirring and cooling (>17°). After being kept overnight the mixture was heated to the b. p. and filtered. The colourless filtrate was concentrated under reduced pressure to 400 ml. and acidified to pH 2. Continuous ether-extraction for 24 and 48 hr. periods afforded extracts 1 (5·38 g.) and 2 (2·22 g.) as crystalline solids heavily contaminated with brown oils. Treatment of extract 1 with boiling ethyl acetate (100 ml.) left undissolved a colourless solid (*a*) (0·163 g.; m. p. 212° with gas evolution). The solution on cooling deposited crystals (*b*) (0·635 g.; m. p. 180—185°). Concentration of the mother-liquor to 20 ml. (charcoal) gave crystals (*c*) (0·296 g.; 186° with gas evolution). After the evaporation of all the solvent the oily residue was extracted with ether (80 ml.). Evaporation of the solution afforded a colourless solid (*d*) (0·725 g.; m. p. *ca.* 100°). No further crystalline material could be obtained by solvent treatment.

Fraction (*a*) was identical (mixed m. p.) with the less-soluble portion of fraction (*c*) (see below). Crystallisation of the combined solids from ethyl acetate gave *2-carboxymethyl-4 : 6-dimethoxyphenylglyoxylic acid* (0·193 g.) as plates, m. p. 212—212·5° (with gas evolution) [Found: C, 53·45; H, 4·65; MeO, 20·2%; equiv. (by titration), 131·9; *M*, 270. $C_{12}H_{12}O_7$ requires C, 53·75; H, 4·5; MeO, 23·1%; equiv. (as dibasic acid), 134·1; *M*, 268·2]. Crystallisation of fraction (*b*) from ethyl acetate gave succinic acid (0·414 g.) as plates, m. p. 184—185°, which did not depress the m. p. (185—186°) of an authentic specimen. The infrared spectra of the two compounds were identical. Crystallisation of fraction (*c*) from ethyl acetate afforded a crystalline solid (0·095 g.), m. p. 212° (with gas evolution), identical with fraction (*a*). Concentration of the mother-liquor gave more succinic acid (0·086 g.). Fraction (*d*) on crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave oxalic acid (0·374 g.) as thick needles, m. p. 102° (with loss of water) [Found: equiv. (by titration), 62·1. Calc. for $C_2H_6O_6$: equiv. (as dibasic acid), 63·05]. The behaviour on melting and the infrared spectrum were identical with those of an authentic specimen. Addition of light petroleum (b. p. 60—80°) to a solution of extract 2 in ethyl acetate gave oxalic acid (0·246 g.), m. p. 100—102° (with loss of water) (Found: equiv., 63·4), as the sole crystalline product.

3 : 5-Dimethoxyphenylacetic Acid.—To a suspension of 3 : 5-dimethoxybenzoic acid (18·2 g.) in dry benzene (60 ml.) was added pure thionyl chloride (47·6 g.) and dry pyridine (0·25 ml.), and the mixture was kept at 50° for 3 hr. The solvent was removed under reduced pressure, finally at 50°; dry benzene (2 × 30 ml.) was added and the distillation was repeated. A solution of the crude acid chloride in dry ether (75 ml.) was added to a dry solution of distilled diazomethane [from *N*-nitrosomethylurea (65 g.), ether (600 ml.), and 50% aqueous potassium hydroxide (190 ml.)] in ether (500 ml.) at 5—10°. After being kept overnight at room temperature the solution was filtered and evaporated under reduced pressure, finally at 30°. A solution of the residual crystalline diazo-ketone in pure dioxan (120 ml.) was added dropwise with stirring to a mixture of silver oxide (2·5 g.), sodium carbonate (7 g.), and sodium thiosulphate (4 g.) in water (250 ml.) at 50—60°. After 1 hr., more silver oxide (4·6 g.) was added and the mixture was stirred at 70° for a further 6 hr., after which there was no evolution of nitrogen on testing with hydrochloric acid. The mixture was cooled, filtered, acidified with dilute nitric acid, and kept at 0° overnight, a crystalline solid (2·1 g.; m. p. 101—102°) separating. Ether-extraction of the filtrate gave a solid (9·4 g.; m. p. 87—92°). Repeated crystallisation of the combined solids from water gave 3 : 5-dimethoxyphenylacetic acid (7·12 g.), m. p. 104—104·5 [Found: C, 61·15; H, 6·3; MeO, 29·9%; equiv. (by titration), 198·3; *M*, 189. Calc. for $C_{10}H_{12}O_4$: C, 61·2; H, 6·15; MeO, 31·65%; equiv., 196·2; *M*, 196·2], ultraviolet absorption max. in EtOH at 2765 Å (ε 1600), inflection at 2210 Å (ε 9100), strong infrared absorption band at 1694 cm.$^{-1}$ (carbonyl group of substituted phenylacetic acid). A m. p. of 100—102° is recorded [8] for a specimen prepared from 3 : 5-dimethoxybenzoic acid by a different homologation route.

2-Carboxymethyl-4 : 6-dimethoxyphenylglyoxylic Acid.—3 : 5-Dimethoxyphenylacetic acid (3·6 g.) was added to a solution of distilled diazomethane [from *N*-nitrosomethylurea (7·5 g.), 50% aqueous potassium hydroxide (25 ml.), and ether (75 ml.)] in ether (75 ml.). After ½ hr. the solution was filtered and evaporated. The residue was dried by adding benzene (20 ml.) and removing this by distillation, finally under reduced pressure. Freshly powdered anhydrous aluminium chloride (5 g.) was added during ½ hr. in small portions with stirring and ice-cooling to a solution of the methyl ester and ethoxalyl chloride [4] (2·5 g.) in nitrobenzene (25 ml.).

[8] Shepard, Porter, Noth, and Simmans, *J. Org. Chem.*, 1952, **17**, 568.

The dark-red mixture was stirred at 0° for a further ½ hr., kept overnight at room temperature, and decomposed with ice and concentrated hydrochloric acid. After distillation with steam to remove nitrobenzene the cooled solution was extracted thoroughly with ether. The extract was washed with sodium hydrogen carbonate solution and the latter separated and made acid. Thorough ether-extraction gave a solid (3·3 g.) which after crystallisation from ethyl acetate containing a little ethanol gave 2-carboxymethyl-4 : 6-dimethoxyphenylglyoxylic acid as colourless plates, m. p. 211—211·5° (with gas evolution), ultraviolet absorption max. in EtOH at 2320, 2760, and 3080 Å (ε 10,700, 8300, and 6800) which did not depress the m. p. (212—212·5° with gas evolution) of the specimen obtained by the oxidation of *OO*-dimethylcurvularin. The infrared spectra of the two compounds were identical in every respect.

2-Carboxymethyl-4 : 5-dimethoxyphenylglyoxylic Acid.—Homoveratric acid on treatment as in the previous experiment gave *2-carboxymethyl-4 : 5-dimethoxyphenylglyoxylic acid* (46%) as laths (from ethyl acetate), m. p. 198·5—199° (with gas evolution) [Found: C, 53·45; H, 4·4%; equiv. (by titration), 133; *M*, 270. $C_{12}H_{12}O_7$ requires C, 53·75; H, 4·5%; equiv. (as dibasic acid), 134·1; *M*, 268·2]. No reaction occurred when anhydrous stannic chloride was substituted for aluminium chloride as catalyst, presumably because of complex formation [9] with the ester groups of the reactants.

2 : 4-Dimethoxy-6-methylacetophenone.—A solution of anhydrous stannic chloride (32·6 g.) in dry benzene (100 ml.) was added dropwise with stirring at 0° to a solution of *OO*-dimethylorcinol (15 g.) and acetyl chloride (7·75 g.) in the same solvent (120 ml.) during 1 hr. After being stirred for 2 hr. at 0° and for 4 hr. at room temperature, the mixture was decomposed with ice and concentrated hydrochloric acid. Ether-extraction afforded, after removal of the solvents, 2 : 4-dimethoxy-6-methylacetophenone (13·2 g.), b. p. 98·5—99·5°/0·2 mm., n_D^{18} 1·5357, which solidified and then crystallised from light petroleum (b. p. 40—60°) in rods, m. p. 41·5—41·7° (Found: C, 68·05; H, 7·25; MeO, 32·55%; *M*, 180. Calc. for $C_{11}H_{14}O_3$: C, 68·05; H, 7·25; MeO, 31·95%; *M*, 194·2). Tambor [10] records m. p. 48° for a specimen prepared in unspecified yield by using anhydrous aluminium chloride as catalyst.

Miscellaneous Derivatives.—2 : 4-Dimethoxyacetophenone (b. p. 97—98°/0·2 mm.) was prepared by the methylation of 2 : 4-dihydroxyacetophenone (m. p. 145—146°). 2 : 4-Dimethoxyphenylglyoxylic acid [11] and 2 : 4-dihydroxy-6-methylacetophenone [12] had m. p.s 109—110·5° and 159—160° respectively. 3 : 4-Dimethoxyacetophenone (b. p. 174·5—175°/16 mm., m. p. 45—46°) was obtained from the stannic chloride-catalysed reaction between acetyl chloride and veratrole (cf. the preparation of 2 : 4-dimethoxy-6-methylacetophenone). 2- and 4-Acetoxyacetophenone [13, 14] had m. p.s 88·5—89° and 53—54° respectively.

I am grateful to Dr. G. McCallum for determining the infrared spectra and to Dr. J. M. C. Thompson for his interest and advice.

Research Department, Imperial Chemical Industries Limited, Nobel Division, Stevenston, Ayrshire. [*Received, September 17th*, 1956.]

[9] *E.g.*, Heiber and Reindl, *Z. Elektrochem.*, 1940, **46**, 559.
[10] Tambor, *Ber.*, 1908, **41**, 793.
[11] Bouveault, *Bull. Soc. chim. France*, 1897, **17**, 946.
[12] Hoesch, *Ber.*, 1915, **48**, 1122.
[13] Friedlaender and Neudörfer, *Ber.*, 1897, **30**, 1077.
[14] Irvine and Robinson, *J.*, 1927, 2086.

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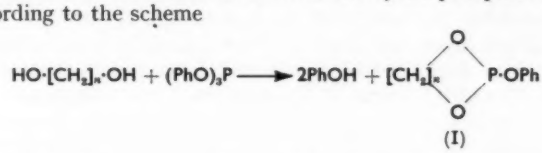
219. *The Organic Chemistry of Phosphorus. Part V.* The Ester-interchange Reaction between Triphenyl Phosphite and Glycols.*

By D. C. Ayres and H. N. Rydon.

Glycols undergo ester-interchange with triphenyl phosphite with the formation of cyclic phosphites, *e.g.* (I). As the separation of the hydroxyl groups increases the yield of cyclic phosphite decreases and increasing amounts of polymeric products are formed. Treatment of the cyclic phosphites with halogens yields halogenoalkyl phenyl phosphorohalidates, while oxidation yields cyclic phosphates. Light-absorption data for the cyclic phosphites and phosphates are recorded and discussed.

Landauer and Rydon [1] drew attention to the great ease with which triphenyl phosphite underwent ester-interchange with alcohols, and postulated the intervention of this reaction in one of their new methods for the preparation of alkyl halides.[2] The present study, which was prompted by difficulties encountered in attempts to prepare halogenohydrins from glycols by the new methods,[1,2] is concerned with ester-interchange between triphenyl phosphite and glycols.

The initial experiments were carried out with ethylene glycol and trimethylene glycol, both of which react with triphenyl phosphite without added catalyst, the former at room temperature, but the latter with reasonable speed only at 100°, with liberation of two mols. of phenol. In both cases substantial amounts of the cyclic phosphite (I; $n = 2$ and 3) were formed according to the scheme



(I)

The cyclic phosphites were accompanied by higher-boiling products, clearly mixtures of the same gross composition as (I).

Further investigation showed that the reaction with ethylene glycol resembled the ester-interchange reactions of silicates [3,4] in being catalysed by both acid (hydrogen chloride) and base (sodium glycoxide), the former increasing, and the latter decreasing, the rate; both catalysts increased the yield of cyclic phosphite as compared with that of the polymeric material, the glycoxide being the more effective.

For preparative purposes the glycoxide is very convenient and a number of glycols have been caused to react with one mol. of triphenyl phosphite in the presence of catalytic amounts of the corresponding sodium glycoxide. The yields of phenol and of cyclic phosphite so obtained are given in Table 1.

In the aliphatic series the yields of cyclic phosphite show the expected dependence on the degree of separation of the reacting hydroxyl groups, the yield of cyclic phosphite steadily decreasing as n in (I) increases from 2 (five-membered ring) to 5 (8-membered ring), while the 9-membered cyclic phosphite (I; $n = 6$) is not formed at all under our conditions; a similar effect has been observed [5] in the analogous reaction of glycols with phosphorus trichloride.

* Part IV, Coe, Rydon, and Tonge, *J.*, 1957, 323.

[1] Landauer and Rydon, *J.*, 1953, 2224.
[2] Cf. Coe, Landauer, and Rydon, *J.*, 1954, 2281.
[3] Peppard, Brown, and Johnson, *J. Amer. Chem. Soc.*, 1946, **68**, 73.
[4] Helferich and Reimann, *Chem. Ber.*, 1947, **80**, 163.
[5] Arbuzov, Zoroastrova, and Rizpolozhenskii, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1948, 208; Arbuzov and Zoroastrova, *ibid.*, 1952, 770.

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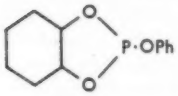
As expected, the reaction is controlled by the stereochemical configurations of the reacting hydroxyl groups. Of the two *cyclo*pentane-1 : 2-diols, only the *cis*, with favourably placed hydroxyl groups, gives a cyclic phosphite, none being formed from the *trans* compound. On the other hand, both *cis*- and *trans-cyclo*hexane-1 : 2-diol give cyclic phosphites and there is no obvious difference in the ease with which the two reactions proceed. Inspection of models shows that, owing to the size of the phosphorus atom, the phosphite ring can be formed readily from both the *cis*-diol, with one axial and one equatorial hydroxyl, and the *trans*-diol, with two equatorial hydroxyl groups. Neither of the two stereoisomeric (*cis* and *trans*) cyclic phosphites (II) is greatly strained and their formation can require little or no distortion of the *cyclo*hexane ring from its preferred chair conformation.



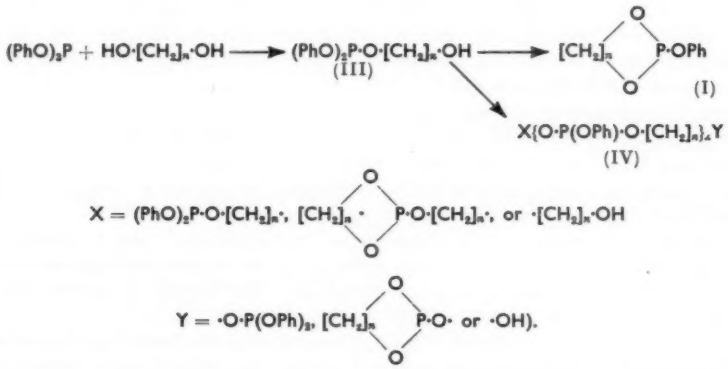
(II)

TABLE 1.

Glycol	Yield: Phenol (mols.)	Yield: Cyclic phosphite (%)	Glycol	Yield: Phenol (mols.)	Yield: Cyclic phosphite (%)
Ethylene glycol	1·96	60	Hexane-1 : 6-diol	1·02 *	0
Propane-1 : 2-diol	1·98	52	*cis-cyclo*Pentane-1 : 2-diol	1·76	49
Propane-1 : 3-diol	1·76	53	*trans-cyclo*Pentane-1 : 2-diol	1·90	0
Butane-1 : 4-diol	2·00	20	*cis-cyclo*Hexane-1 : 2-diol...	1·82	33
Pentane-1 : 5-diol	1·92	13	*trans-cyclo*Hexane-1 : 2-diol	1·86	29

* Considerable loss during working-up.

Attempts to establish the nature of the high-boiling by-products of the interchange reaction, which ranged from oils (from the lower glycols) to a rubber-like solid (from hexane-1 : 6-diol), were frustrated by formidable difficulties in separation, analysis, and characterisation. The likely course of the reaction is the following :

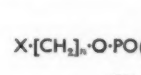


The initial intermediate (III) undergoes either intramolecular ester-interchange to the cyclic phosphite (I), or further intermolecular ester-interchange with eventual formation of polymer (IV). The consistent production of two mols. of phenol indicates that only very small amounts of free hydroxyl can be present in the polymers.

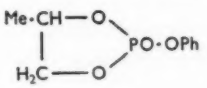
The ester-interchange between triphenyl phosphite and glycerol gave only polymeric material; this is expected in view of the presence of a free hydroxyl group in the cyclic phosphite, which will inevitably lead to further interchange and consequent polymer formation.

On treatment with bromine, ethylene phenyl phosphite (I; $n = 2$) yields the 2-bromoethyl phosphorobromidate (V; $n = 2$; X = Y = Br), characterised as the derived

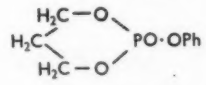
anilide (V; $n = 2$; X = Br; Y = NHPh); trimethylene phenyl phosphite and chlorine similarly yield the 3-chloropropyl compound (V; $n = 3$; X = Y = Cl). The formation of halogeno-alkyl phosphorohalidates, such as (V), by way of the cyclic phosphites (I) explains the very poor yields obtained in attempts to prepare halogenohydrins from glycols by reaction with triphenyl phosphite and alkyl halides [1] or halogens.[2]



(V)



(VI)



(VII)

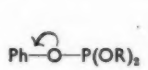
Oxidation of propylene and trimethylene phenyl phosphites gave the corresponding cyclic phosphates, *viz.*, propylene phenyl phosphate (VI) and trimethylene phenyl phosphate (VII). These two compounds differ remarkably in their stability to hydrolysis, the latter crystallising unchanged from boiling water whereas the former is readily hydrolysed by water.

TABLE 2. *Light absorption of some phosphites and phosphates.* $\lambda_{max.}$ (mμ) *and* $\varepsilon_{max.}$ (*in parentheses*).

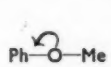
Phosphites			
Ethylene phenyl phosphite	265·5 (970)	270 (1160)	277·5 (1155)
Phenyl propylene phosphite	265·5 (1110)	270 (1440)	277·5 (1510)
Phenyl trimethylene phosphite	264·5 (970)	270·5 (1095)	277 (1010)
Phenyl tetramethylene phosphite	266·5 (760) *	270·5 (1005)	277 (990)
Pentamethylene phenyl phosphite	266·5 (840) *	270 (990)	277 (710)
*cis-cyclo*Pent-1 : 2-ylene phenyl phosphite	266 (910)	271 (1090)	277 (1110)
*cis-cyclo*Hex-1 : 2-ylene phenyl phosphite	266 (910)	270·5 (990)	277 (770)
*trans-cyclo*Hex-1 : 2-ylene phenyl phosphite	265·5 (905)	269 (840) *	—
Triphenyl phosphite	265 (1780)	270 (1870)	278 (1120)
Phosphates			
Phenyl propylene phosphate †	258 (300) *	263 (380)	268 (385)
Phenyl trimethylene phosphate †	256 (355)	262 (430)	268 (330)
Triphenyl phosphate	256 (960)	262 (1180)	268 (910)
Reference compounds			
Anisole	265 (1120)	271 (1580)	278 (1450)
Phenyl acetate [7]	—	262 (250)	—
Benzene	249 (175)	255 (230)	261 (150)

* Inflexion on shoulder. † In ethanol; all others in hexane.

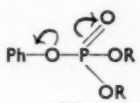
Light-absorption data for the cyclic phosphites and phosphates, together with those for the corresponding triphenyl esters, are collected in Table 2; full curves are given by Ayres.[6] All the phosphites have very similar spectra, arising by intensification and bathochromic displacement of the *B*-band system of benzene; [8] a similar effect is shown by anisole and both effects may be ascribed to electron donation from the oxygen atoms (VIII and IX). The effect is very much smaller, although in the same direction,



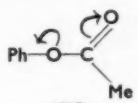
(VIII)



(IX)



(X)



(XI)

in the phosphates; this difference, like the similar one between anisole and phenyl acetate, is clearly due to partial cancellation of the electron drift towards the benzene nucleus by

[6] Ayres, Ph.D. Thesis, Manchester, 1954.
[7] Wolf and Strasser, *Z. phys. Chem.*, 1933, *B*, **21**, 389.
[8] Burawoy, *Ber.*, 1930, **63**, 3157; 1931, **64**, 489; Braude, *Ann. Reports*, 1945, **42**, 105; Burawoy and Chamberlain, *J.*, 1952, 2310.

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the opposing electron shift in the phosphonyl and carbonyl groups (X and XI). The approximate proportionality between the absorption intensities and the number of phenyl groups in the phosphates, but not in the phosphites, may similarly be due to the overwhelming effect of the phosphonyl group in the phosphates.

Experimental

Ester-interchange Reactions.—Unless otherwise stated all products were worked up by direct vacuum distillation.

Ethylene glycol. (*a*) Ethylene glycol (31 g.; 0·5 mole) and triphenyl phosphite (155 g.; 0·5 mole) were shaken together in a stoppered flask; much heat was evolved and the mixture became homogeneous within 1 hr. Distillation gave (i) phenol (92·5 g.; 98%), b. p. 99—115°/37 mm., (ii) crude cyclic phosphite (42 g.; 46%), b. p. 59—61°/0·09 mm., n_D^{20} 1·5356, and (iii) polymeric products (41 g.; 45%), b. p. 61—176°/0·1—0·3 mm., n_D^{20} 1·5070—1·5827. Redistillation of fraction (ii) gave pure *ethylene phenyl phosphite* (I; $n = 2$), b. p. 73°/0·3 mm., n_D^{20} 1·5342 [Found: C, 52·9; H, 4·9; P, 16·4%; equiv. (by hydrol.), 189. $C_8H_9O_3P$ requires C, 52·1; H, 4·9; P, 16·8%; equiv., 184].

(*b*) Four separate portions of triphenyl phosphite (155 g.; 0·5 mole) were mixed with portions of ethylene glycol (31 g.; 0·5 mole), one without addition and the other three containing, respectively, 0·01 mole of sodium glycoxide, sodium phenoxide, and hydrogen chloride. The four mixtures at 37° were shaken by hand for 5 sec. every 10 min. and the time to homogeneity noted; distillation gave ethylene phenyl phosphite. The results were as follows:

Catalyst	Time to homogeneity (min.)	Phosphite Yield (%)	Phosphite n_D^{20}
None	70	23	1·5336
Sodium glycoxide	>300 *	49	1·5366
Sodium phenoxide	70	14	1·5347
Hydrogen chloride	20	33	1·5348

* Completed by heating on steam-bath.

(*c*) The following procedure is the most convenient for preparative purposes: Triphenyl phosphite (155 g.; 0·5 mole) was vigorously stirred on the steam-bath with ethylene glycol (31 g.; 0·5 mole) in which sodium (0·2 g.; 0·01 mole) had been dissolved. Heating and stirring were continued for 1½ hr. after the mixture had become homogeneous. Distillation afforded ethylene phenyl phosphite (55 g.; 60%), b. p. 70—76°/0·2 mm., n_D^{20} 1·5370.

Propylene glycol. (*a*) Triphenyl phosphite (155 g.; 0·5 mole) was stirred on the steam-bath with the glycol (38 g.; 0·5 mole) in which sodium (0·2 g.; 0·01 mole) had been dissolved. Stirring was continued for 2 hr. after homogeneity was attained (10 min.). Distillation gave phenol (93·3 g.; 99%) and the cyclic phosphite (51·5 g.; 52%), b. p. 81—87°/0·6 mm., n_D^{20} 1·5155; redistillation gave pure *phenyl propylene phosphite*, b. p. 76°/0·4 mm., n_D^{20} 1·5198 (Found: C, 53·7; H, 5·2. $C_9H_{11}O_3P$ requires C, 54·5; H, 5·6%).

(*b*) Repetition of the above preparation with more sodium (6·9 g.; 0·3 mole) gave the same phosphite (49·5 g.; 50%), b. p. 82—90°/0·3 mm.

(*c*) Propylene phosphorochloridite[9] (124 g.; 0·88 mole) and dimethylaniline (109 g.; 0·9 mole) in ether (100 ml.) were treated during 30 min., with stirring and ice-cooling, with phenol (83 g.; 0·88 mole) in ether (75 ml.). After being stirred for a further 2 hr. the product was filtered and distilled, yielding phenyl propylene phosphite (113 g.; 65%), b. p. 94°/2 mm., n_D^{22} 1·5192.

Trimethylene glycol. (*a*) Triphenyl phosphite (103·3 g.; 0·33 mole) was heated on the steam-bath with the glycol (25·3 g.; 0·33 mole) for 6 hr. with intermittent shaking. Distillation gave (i) phenol (55 g.; 88%), b. p. 85—90°/21—25 mm., (ii) crude cyclic phosphite (18 g.; 27%), b. p. 69—75°/0·07 mm., n_D^{20} 1·5265, and (iii) polymeric material (38 g.; 58%), b. p. 165—173°/0·05—0·1 mm., n_D^{20} 1·5576. Redistillation of fraction (ii) gave pure *phenyl trimethylene phosphite* (I; $n = 3$), b. p. 88°/0·4 mm., n_D^{20} 1·5337 (Found: C, 54·8; H, 5·8.

[9] Lucas, Mitchell, and Scully, *J. Amer. Chem. Soc.*, 1950, **72**, 5491.

$C_9H_{11}O_3P$ requires C, 54·5; H, 5·6%); this crystallised after some months (m. p. 44—46°, not raised on recrystallisation from acetone–hexane); the supercooled melt had n_D^{27} 1·5230.

(*b*) Repetition with more glycol (50·6 g.; 0·66 mole) gave the same phosphite, b. p. 68—76°/0·05 mm., n_D^{18} 1·5286, in much reduced yield (4·6 g.; 7%).

(*c*) Triphenyl phosphite (155 g.; 0·5 mole), stirred on the steam-bath for 2 hr. with sodium (0·2 g.; 0·01 mole) dissolved in trimethylene glycol (38 g.; 0·5 mole), gave the best yield of phenyl trimethylene phosphite (52·5 g.; 53%), b. p. 89°/0·4 mm., m. p. 38—42° [Found: equiv. (by hydrol.), 207. $C_9H_{11}O_3P$ requires equiv., 198].

Butane-1 : 4-*diol*. (*a*) Triphenyl phosphite (62 g.; 0·2 mole), stirred on the steam-bath for 1½ hr. with sodium (0·2 g.; 0·01 mole) dissolved in the glycol (18 g.; 0·2 mole), gave phenol (38 g.; 100%), b. p. 85°/0·3 mm., and the crude cyclic phosphite (8·6 g.; 20%), b. p. 91—95°/0·3 mm., n_D^{22} 1·5359. Redistillation gave pure *phenyl tetramethylene phosphite* (I; $n = 4$), b. p. 94°/0·3 mm., n_D^{22} 1·5361 (Found: C, 56·7; H, 6·3. $C_{10}H_{13}O_3P$ requires C, 56·6; H, 6·1%).

(*b*) A similar experiment without sodium gave less (5·2 g.; 12%) phosphite, b. p. 90°/0·8 mm., n_D^{20} 1·5336.

Pentane-1 : 5-*diol*. Triphenyl phosphite (74·2 g.; 0·24 mole), the glycol (25 g.; 0·24 mole), and sodium (0·2 g.; 0·01 mole) gave phenol (43·4 g.; 96%) and cyclic phosphite (7·3 g.; 13%), b. p. 98—104°/0·0015 mm., n_D^{18} 1·5268—1·5346; redistillation gave pure *pentamethylene phenyl phosphite* (I; $n = 5$), b. p. 99°/0·0015 mm., n_D^{17} 1·5237 (Found: P, 13·2. $C_{11}H_{15}O_3P$ requires P, 13·7%).

Hexane-1 : 6-*diol*. The glycol (14·8 g.; 0·125 mole) containing dissolved sodium (0·2 g.; 0·01 mole) was added in portions during 75 min. to stirred triphenyl phosphite (38·8 g.; 0·125 mole) at 90°. After each addition the temporary clouding of the mixture cleared rapidly. After being left overnight the product was a rubber-like mass, insoluble in ether and dioxan, which dissolved slowly in boiling chloroform. Distillation of the chloroform solution gave some phenol (12 g.; 51%) at a bath temp. of 130°/0·3 mm.; raising the bath temp. to 180°/0·004 mm. caused a little more phenol to sublime but the remaining product showed no signs of boiling.

cis-cyclo*Pentane*-1 : 2-*diol*. Sodium (0·2 g.; 0·01 mole) was dissolved in the glycol [10] (10 g.; 0·1 mole); after addition of triphenyl phosphite (31 g.; 0·1 mole), the mixture rapidly became homogeneous, without external heating. Distillation gave (i) phenol (16·5 g.; 88%), (ii) cyclic phosphite (10·9 g.; 49%), b. p. 72—75°/0·002 mm., n_D^{23} 1·5266, and (iii) polymeric material (3·6 g.; 16%), b. p. 120—130°/0·0015 mm., n_D^{23} 1·5780. Redistillation of fraction (ii) gave pure cis-cyclo*pent*-1 : 2-*ylene phenyl phosphite*, b. p. 68°/0·007 mm., n_D^{20} 1·5240 (Found: P, 14·2. $C_{11}H_{13}O_3P$ requires P, 13·8%).

trans-cyclo*Pentane*-1 : 2-*diol*. The glycol [10] (10 g.; 0·1 mole) was treated with sodium and triphenyl phosphite as for the cis-*isomer*; homogeneity was attained after 10 min. on the steam-bath. Distillation gave phenol (17·8 g.; 95%) and left a very viscous, ether-insoluble residue which showed no signs of distillation at 0·008 mm. from a bath at 200°.

cis-cyclo*Hexane*-1 : 2-*diol*. Sodium (0·2 g.; 0·01 mole) was added to the glycol [11] (11·6 g.; 0·1 mole) in dioxan (30 ml.). When dissolution was complete the solvent was removed under reduced pressure and the residue stirred with triphenyl phosphite (31 g.; 0·1 mole) until homogeneous (15 min.). Phenol (17·1 g.; 91%) was distilled off at 80°/0·2 mm. and the residue stirred into light petroleum (b. p. 40—60°), high-polymeric material (4·8 g.; 20%) remaining undissolved. Distillation of the soluble material gave (i) crude cyclic phosphite (8·8 g.; 37%), b. p. 96—112°/0·004 mm., and (ii) polymeric material (6·1 g.; 26%), b. p. 120—133°/0·003 mm. Fraction (i) partially crystallised; redistillation of the solid (7·8 g.%; 33%) afforded pure cis-cyclo*hex*-1 : 2-*ylene phenyl phosphite* (II), b. p. 97°/0·004 mm., m. p. 43—45° (Found: C, 61·1; H, 7·0; P, 12·8. $C_{12}H_{15}O_3P$ requires C, 60·5; H, 6·3; P, 13·0%).

Hydrolysis with boiling 4N-hydrochloric acid for 4 hr. gave 88% of *cis-cyclo*hexane-1 : 2-diol, m. p. and mixed m. p. 86—89°, characterised as the ditoluene-*p*-sulphonate,[12] m. p. and mixed m. p. 127—129°.

trans-cyclo*Hexane*-1 : 2-*diol*. The glycol [13] (11·6 g.; 0·1 mole), treated similarly, but without the treatment with light petroleum, gave (i) phenol (17·4 g.; 93%), (ii) crude cyclic

[10] Owen and Smith, *J.*, 1952, 4026.
[11] Clarke and Owen, *J.*, 1949, 315.
[12] Criegee and Stanger, *Ber.*, 1936, **69**, 2754.
[13] Roebuck and Adkins, *Org. Synth.*, 1948, **28**, 35.

phosphite (7·0 g.; 29%), b. p. 82—100°/0·0045 mm., n_D^{37} 1·5320—1·5360, and (iii) polymeric material (2·1 g.; 9%). Pure trans-cyclo*hex*-1 : 2-*ylene phenyl phosphite* (II) had b. p. 84°/0·0045 mm., n_D^{37} 1·5330 (Found: C, 60·6; H, 6·7; P, 13·1%).

Hydrolysis by boiling 4N-hydrochloric acid for 6 hr. gave 91% of *trans-cyclo*hexane-1 : 2-diol, m. p. and mixed m. p. 100—102°, characterised as the ditoluene-*p*-sulphonate,[12] m. p. and mixed m. p. 104—105°.

Glycerol. Sodium (0·2 g.; 0·01 mole) was dissolved in glycerol (46 g.; 0·5 mole) and the solution stirred on the steam-bath with triphenyl phosphite (155 g.; 0·5 mole) until homogeneous (5 hr.). Distillation afforded phenol (132·7 g.; 94%) and an extremely viscous residue (62 g.; 103%), soluble only in chloroform, which decomposed on attempted distillation. The polymer dissolved completely on boiling for a few min. with 2N-hydrochloric acid or with 2N-sodium hydroxide.

Reactions of Cyclic Phosphites.—(i) *With halogens.* (*a*) *Ethylene phenyl phosphite and bromine.* Bromine (26·6 g.; 0·16 mole) was added during 1 hr., with ice-cooling, to the stirred phosphite (30·6 g.; 0·16 g.), moisture being rigorously excluded. After removal of a little unconsumed bromine in a stream of dry air, a portion (2·1 g.) of the residual phosphorobromidate was added to aniline (1·13 g.) at 0°; benzene (5 ml.) was added and the mixture warmed for 20 min. Aniline hydrobromide was filtered off and washed with hot benzene (2 × 5 ml.). Evaporation of the benzene solution followed by recrystallisation of the residue from aqueous ethanol gave 2-*bromoethyl phenyl* N-*phenylphosphoramidate* (V; $n = 2$; X = Br, Y = NHPh) (0·85 g.; 40%), m. p. 128° (Found: N, 4·2; Br, 22·0. $C_{14}H_{15}O_3NBrP$ requires N, 3·9; Br, 22·5%).

(*b*) *Trimethylene phenyl phosphite and chlorine.* Chlorine (1·1 g.) was passed into an ice-cooled solution of the phosphite (3·3 g.) in chloroform (20 ml.). This solution was then added dropwise, with stirring and ice-cooling, to aniline (3·1 g.) in chloroform (20 ml.). After 2 hr. aniline hydrochloride was filtered off and the filtrate washed with water until free from chloride ion. Evaporation of the dried solution gave 3-*chloropropyl phenyl* N-*phenylphosphoramidate* (V; $n = 3$; X = Cl; Y = NHPh) (4·8 g.; 89%), m. p. 65° after recrystallisation from aqueous ethanol (Found: N, 4·3. $C_{15}H_{17}O_3NClP$ requires N, 4·3%).

(ii) *Oxidation.* (*a*) *Phenyl propylene phosphite.* The phosphite (13·2 g.) in dry benzene (35 ml.) was stirred for 40 min. with yellow mercuric oxide (16 g.); the vigorous reaction caused the benzene to boil. After filtration and centrifugation to remove mercury and unconsumed mercuric oxide, distillation afforded *phenyl propylene phosphate* (VI) (3·1 g.; 22%), an oil, b. p. 123°/0·007 mm., n_D^{20} 1·5068 (Found: P, 14·4. $C_9H_{11}O_4P$ requires P, 14·5%). This phosphate is readily soluble in ether; it dissolves in water, with evolution of heat, to form a strongly acid solution from which it cannot be recovered unchanged.

(*b*) *Phenyl trimethylene phosphite.* The cyclic phosphite (9·9 g.) in dry benzene (40 ml.) was added during 1 hr. to a cooled and stirred suspension of active manganese dioxide [14] (45 g.) in dry benzene (60 ml.). After 24 hr. the mixture was filtered, the solid being washed with benzene (3 × 30 ml.). Evaporation of the filtrate and washings gave *phenyl trimethylene phosphate*, (VII), (6·0 g.; 56%), m. p. 71—74°, raised to 76—77° by recrystallisation from carbon tetrachloride containing a little chloroform (Found: C, 50·9; H, 5·5. $C_9H_{11}O_4P$ requires C, 50·5; H, 5·15%). The phosphate is insoluble in light petroleum, slightly soluble in ether and carbon tetrachloride and very soluble in benzene, ethyl acetate, and chloroform; it dissolves readily in boiling water, giving a neutral solution from which it crystallises unchanged on cooling.

We thank the Ministry of Education for a maintenance grant (to D. C. A.), Dr. F. Liversedge for measuring the absorption spectra, and Dr. A. Burawoy for helpful advice on their interpretation. Most of the microanalyses were carried out by Mr. V. Manohin.

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MANCHESTER, 1. [*Received, October 17th,* 1956.]

[14] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.

XUM

220. *The Constitution of Aspidospermine. Part II.* Ultraviolet Absorption of the* Bz-*Methoxy-tetra- and -hexa-hydrocarbazoles.*

By J. R. Chalmers, H. T. Openshaw, and G. F. Smith.

The 5-, 6-, 7-, and 8-methoxy-derivatives of tetrahydrocarbazole, hexahydrocarbazole, and 9-acetylhexahydrocarbazole have been prepared and their ultraviolet absorption spectra measured. Comparison with the spectra of aspidospermine and deacetylaspidospermine confirms that the alkaloid is a 7-methoxyindoline derivative.

Aspidospermine, $C_{22}H_{30}O_2N_2$, an alkaloid occurring in *Aspidosperma quebracho blanco* and *Vallesia glabra*, contains an acetamido-group, N(*a*)Ac, and a tertiary, basic nitrogen atom, N(*b*).[1] By distillation with zinc dust Witkop [2] obtained 3 : 5-diethylpyridine and an indole fraction (probably a mixture of 3-ethyl- and 3-methyl-indole). A study of the ultraviolet absorption spectra and colour reactions of aspidospermine and deacetylaspidospermine indicated that these bases are dihydroindoles rather than indoles,[2,3,4] and also showed that the acetylated nitrogen is directly attached to the aromatic ring. Aspidospermine also contains an aromatically bound methoxyl group, since hot hydriodic acid brings about deacetylation and demethylation and yields a phenolic base, aspidosine.[1]

Warnat [5] established the orientation of the methoxyl group in the dihydroindole alkaloids α- and β-colubrine by oxidation to the corresponding methoxy-*N*-oxalylanthranilic acids, but we have been unsuccessful in applying this method to aspidospermine. We therefore undertook the preparation of the four isomeric hexahydro-*Bz*-methoxycarbazoles and their *N*-acetyl derivatives, and the comparison of their absorption spectra with those of aspidospermine and deacetylaspidospermine.

When this work was undertaken, the only tetrahydro-*Bz*-methoxycarbazole known was the 6-isomer.[6] 1 : 2 : 3 : 4-Tetrahydro-8-methoxycarbazole was prepared by the action of hot glacial acetic acid on *cyclo*hexanone *o*-methoxyphenylhydrazone. Similar treatment of *cyclo*hexanone *m*-methoxyphenylhydrazone gave a mixture, separable by crystallisation and picrate formation, of the 5- and the 7-methoxy-isomer; the preponderant isomer was shown to be the 7-methoxy-compound by the resemblance of its absorption spectrum to that of tetrahydroharmine [7] and through the degradation of the derived *N*-acetylhexahydromethoxycarbazole described below. Recently, Cummins and Tomlinson [8] have prepared 1 : 2 : 3 : 4-tetrahydro-5-methoxycarbazole by an unequivocal method, and have also described an independent synthesis of the 7-methoxy-isomer, and their results confirm our assignment of structure. The ultraviolet absorption spectra of the isomeric tetrahydromethoxycarbazoles, shown in Fig. 1, are sufficiently different to afford a means of determining the position of a methoxyl group in a methoxyindole alkaloid of unknown structure; this method has been applied, for example, to reserpine [7] and ibogaine.[9]

Reduction of the tetra- to the hexa-hydrocarbazoles was achieved electrolytically or by means of tin and hydrochloric acid. The products are assumed to be the *cis*-isomers.[10] The absorption spectra of the hexahydromethoxycarbazoles and their *N*-acetyl derivatives

* Part I, Openshaw and Smith, *Experientia*, 1948, **4**, 428.

[1] Ewins, *J.*, 1914, **105**, 2738.
[2] Witkop, *J. Amer. Chem. Soc.*, 1948, **70**, 3712.
[3] Raymond-Hamet, *Compt. rend.*, 1948, **226**, 2154.
[4] Openshaw and Smith, *Experientia*, 1948, **4**, 428.
[5] Warnat, *Helv. Chim. Acta*, 1931, **14**, 997.
[6] Borsche, Witte, and Bothe, *Annalen*, 1908, **359**, 49.
[7] Dorfman, Furlenmeier, Huebner, Lucas, MacPhillamy, Mueller, Schlittler, Schwyzer, and St. André, *Helv. Chim. Acta*, 1954, **37**, 59.
[8] Cummins and Tomlinson, *J.*, 1955, 3475.
[9] Schlittler, Burckhardt, and Gellert, *Helv. Chim. Acta*, 1953, **36**, 1337.
[10] Gurney, Perkin, and Plant, *J.*, 1927, 2676.

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FIG. 1.

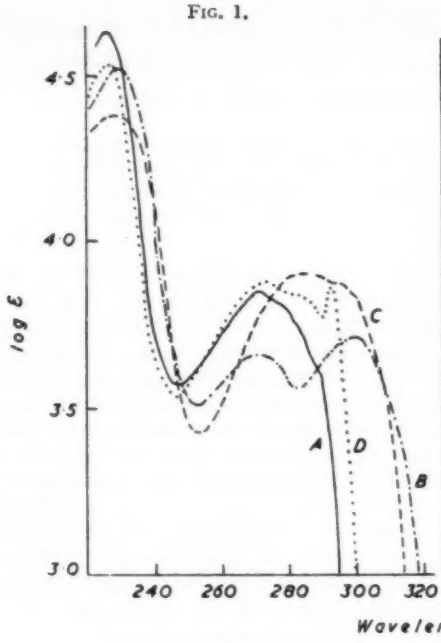


FIG. 2.

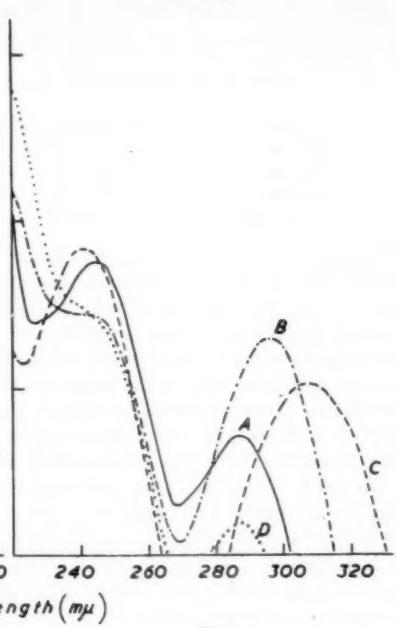


FIG. 3.

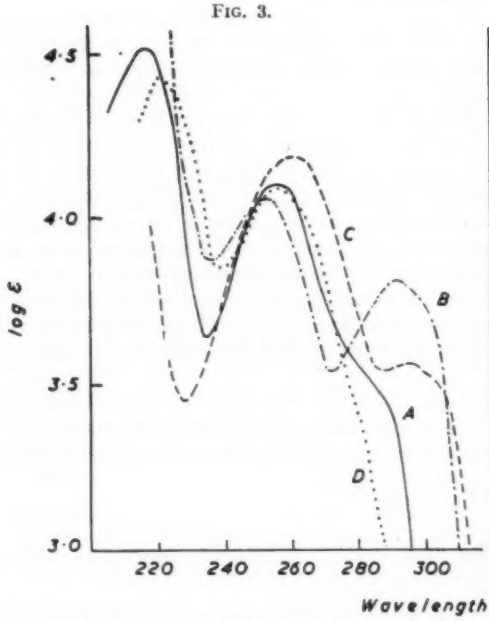


FIG. 4.

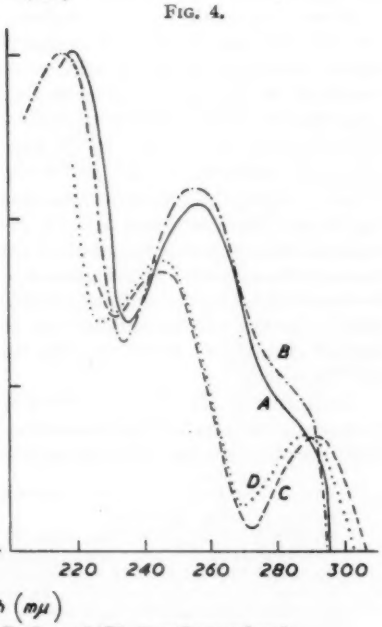
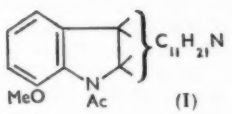


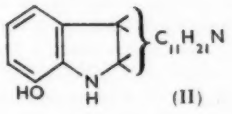
FIG. 1. *Absorption spectra of (A) tetrahydro-8-, (B) -7-, (C) -6-, and (D) -5-methoxycarbazole.*
FIG. 2. *Absorption spectra of (A) hexahydro-8-, (B) -7-, (C) -6-, and (D) -5-methoxycarbazole.*
FIG. 3. *Absorption spectra of (A) 9-acetylhexahydro-8-, (B) -7-, (C) -6-, and (D) -5-methoxycarbazole.*
FIG. 4. *Absorption spectra of (A) aspidospermine, (B) 9-acetylhexahydro-8-methoxycarbazole. (C) deacetylaspidospermine, and (D) hexahydro-8-methoxycarbazole.*

are shown in Figs. 2 and 3. The spectra shown in Fig. 2 show a close correlation with those recorded by Millson and Robinson [11] in their independent but parallel work with the hexahydro-*Bz*-methoxy-9 : 11-dimethylcarbazoles.

A comparison of the ultraviolet spectra of aspidospermine and deacetylaspidospermine with the synthetic 8-methoxy-compound is shown in Fig. 4 and leads to the assignment of the partial structure (I) to aspidospermine. This conclusion has also been reached by Witkop and Patrick [12] through a study of the properties of aspidosine (II), which behaves as an *o*-aminophenol derivative.

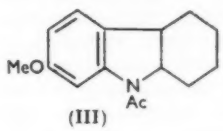


(I)

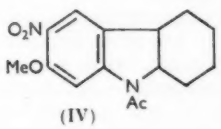


(II)

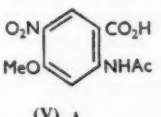
In order to confirm the orientation assigned to hexahydro-7-methoxycarbazole, it was converted into a derivative of 4-methoxyanthranilic acid. Preliminary experiments with the more plentiful 6-methoxy-isomer indicated that oxidation with permanganate caused breakdown of the aromatic nucleus; the principal product isolated was adipic acid. In order to increase the resistance of the aromatic ring to oxidation, 9-acetylhexahydro-7-methoxycarbazole (III) was nitrated, and the resulting mononitro-compound (probably IV) was oxidised. Besides adipic acid (5%), a small yield (2%) was obtained of an acid which did not depress the melting point of the nitration product (probably V) of 2-acetamido-4-methoxybenzoic acid (VI).



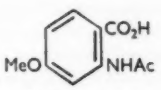
(III)



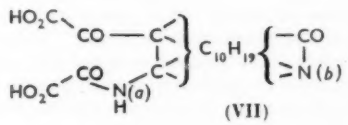
(IV)



(V)



(VI)



(VII)

In an attempt to apply a similar procedure to aspidospermine, the alkaloid was found to be smoothly nitrated to nitroaspidospermine, which on hydrolysis gave deacetylnitroaspidospermine. Oxidation of nitroaspidospermine with barium permanganate gave no methoxynitroanthranilic acid derivative, however; much barium nitrate was formed, indicating extensive breakdown of the aromatic ring. The only other crystalline product was an acid, probably $C_{17}H_{22}O_7N_2$, which may have the structure (VII).

Experimental

Absorption spectra were measured in EtOH.

1 : 2 : 3 : 4-*Tetrahydro-5- and-7-methoxycarbazoles.*—*m*-Methoxyphenylhydrazine [13] (20·15 g.) and *cyclo*hexanone (14·6 g.) were mixed, reaction being exothermic and water separating. Acetic acid (100 ml.) was added, and the mixture was heated to 95°; it was then removed from the steam-bath until the vigorous reaction, which caused the mixture to boil, had slackened; the mixture was then boiled for 10 min., and allowed to cool. The mixed tetrahydrocarbazoles (22·3 g., 75%), m. p. 102—106°, crystallised. A further quantity was obtained by distilling the

[11] Millson and Robinson, *J.*, 1955, 3362.
[12] Witkop and Patrick, *J. Amer. Chem. Soc.*, 1954, **76**, 5603.
[13] Kermack, Perkin, and Robinson, *J.*, 1921, **119**, 1602.

mother-liquor under reduced pressure; after acetic acid and acetamide had been removed, the tetrahydrocarbazoles (4·68 g.) distilled at 220—230°/15 mm., and crystallisation from methanol gave colourless crystals (2·35 g.), m. p. 103—105°.

Crystallisation of the mixture (12 g.) from benzene (25 ml.) gave colourless leaflets (6·3 g.) of 1 : 2 : 3 : 4-tetrahydro-7-methoxycarbazole, m. p. 145—146°. After crystallisation from ethanol and vacuum-sublimation it had m. p. 148°, $\lambda_{max.}$ 229, 270, 300 mμ (ε 33,000, 4500, 5100 respectively) (Cummins and Tomlinson [8] give m. p. 148—149°) (Found : C, 77·6; H, 7·3; N, 7·0. Calc. for $C_{13}H_{15}ON$: C, 77·6; H, 7·5; N, 7·0%). The *picrate*, brown laths from methanol, had m. p. 137° (Found : N, 12·7. $C_{13}H_{15}ON,C_6H_3O_7N_3$ requires N, 13·0%). The benzene mother-liquor was concentrated and treated with alcoholic picric acid; the black, sparingly-soluble *picrate* of 1 : 2 : 3 : 4-tetrahydro-5-methoxycarbazole (2·4 g.), m. p. 170°, separated; a sample was recrystallised from ethanol without raising the m. p. (Found : C, 52·9; H, 4·1; N, 13·0. $C_{13}H_{15}ON,C_6H_3O_7N_3$ requires C, 53·0; H, 4·2; N, 13·0%). The base recovered from this picrate and crystallised from ethanol had m. p. 129—130°, raised by sublimation in a vacuum to 130—131°, $\lambda_{max.}$ 227, 273, 293 mμ (ε 35,000, 7600, 7400 respectively) (Cummins and Tomlinson [8] give m. p. 126—127°) (Found : C, 77·6; H, 7·4%).

1 : 2 : 3 : 4-*Tetrahydro-8-methoxycarbazole*.—A solution of the syrupy *cyclo*hexanone *o*-methoxyphenylhydrazone [from *cyclo*hexanone (3·5 g.) and *o*-methoxyphenylhydrazine (4·5 g.)] in glacial acetic acid (25 ml.) was cautiously heated to boiling; an exothermic reaction occurred with considerable darkening. The bulk of the acetic acid was distilled off at atmospheric pressure, and the residue was fractionated under reduced pressure; the fraction boiling at 190—205°/15 mm. (3·96 g.) was treated with picric acid (4·5 g.) in ethanol, and the resulting picrate was collected in two crops, (i) m. p. 141—144° (decomp.) (4·0 g.) and (ii) m. p. 139—142° (decomp.) (2·2 g.). Recrystallisation from ethanol gave 1 : 2 : 3 : 4-*tetrahydro-8-methoxycarbazole picrate* as purplish-black needles, m. p. 145—146° (decomp.) (Found : C, 53·4; H, 4·2; N, 12·8. $C_{13}H_{15}ON,C_6H_3O_7N_3$ requires C, 53·0; H, 4·2; N, 13·0%). The base recovered from this picrate was a syrup, b. p. 124°/0·08 mm., $\lambda_{max.}$ 226, 271 mμ (ε 42,000, 7050 respectively).

Hexahydromethoxycarbazoles.—(i) The tetrahydrocarbazole, dissolved in 50% sulphuric acid, was reduced electrolytically [14] at 25°, with lead electrodes and a current density of 0·03 amp./cm.^{2}. Reduction was considered complete when a sample of the catholyte remained clear on dilution with water. The diluted solution was extracted with ether to remove any unchanged tetrahydrocarbazole, after which it was made alkaline with ammonia, and the hexahydrocarbazole was isolated by means of ether. (ii) A mixture of the tetrahydrocarbazole (2 g.), tin (4 g.), ethanol (4 ml.), and concentrated hydrochloric acid (4 ml.) was heated on the steam-bath under reflux for several hours. The solution was decanted from undissolved tin, basified with concentrated aqueous sodium hydroxide, and extracted with ether. The ethereal solution was extracted with N-hydrochloric acid, the extract was basified, and the liberated hexahydrocarbazole was isolated by ether-extraction.

1 : 2 : 3 : 4 : 10 : 11-*Hexahydro-5-methoxycarbazole* distilled at 90° (bath-temp.)/0·005 mm. and formed colourless crystals, m. p. 53—55°, $\lambda_{max.}$ 240 (infl.), 288 mμ (ε 5600, 1270), from light petroleum (b. p. 40—60°) (Found : C, 76·4; H, 8·1; N, 7·2. $C_{13}H_{17}ON$ requires C, 76·8; H, 8·4; N, 6·9%). The *acetyl derivative*, prepared by treatment with acetic anhydride at 100° and purified by removal of unchanged basic material and distillation in a high vacuum, was a colourless gum, $\lambda_{max.}$ 222, 256 mμ (ε 26,000, 12,200) (Found : C, 72·9; H, 7·8; N, 5·7. $C_{15}H_{19}O_2N$ requires C, 73·4; H, 7·8; N, 5·7%).

1 : 2 : 3 : 4 : 10 : 11-*Hexahydro-6-methoxycarbazole*, b. p. 172°/9 mm., $\lambda_{max.}$ 242, 307 mμ (ε 8300, 3200), gave a *picrate*, m. p. 153—154° (Found : C, 53·1; H, 4·9; N, 13·0. $C_{13}H_{17}ON,C_6H_3O_7N_3$ requires C, 52·7; H, 4·6; N, 13·0%), and a *hydrogen oxalate* (from alcohol), m. p. 166—167° (decomp.) (Found : C, 61·1; H, 6·7; N, 4·6. $C_{13}H_{17}ON,C_2H_2O_4$ requires C, 61·4; H, 6·5; N, 4·8%). The *acetyl derivative* formed colourless prisms (from ethanol), m. p. 98—99°, $\lambda_{max.}$ 261, 295 mμ (ε 15,500, 3680) (Found : C, 73·3; H, 7·4; N, 6·0%).

1 : 2 : 3 : 4 : 10 : 11-*Hexahydro-7-methoxycarbazole* distilled at 124°/0·1 mm. and crystallised; its m. p. 30—33° was raised by repeated crystallisation from light petroleum to 37—38°; $\lambda_{max.}$ were 240 (infl.), 297 mμ (ε 5300, 4400) (Found : C, 76·9; H, 8·2; N, 6·7%). It formed a *hydrogen oxalate* (from ethanol), m. p. 183° (Found : C, 61·8; H, 6·4; N, 4·8%), and a rather soluble *picrate* (from methanol), m. p. 139—140° (decomp.) (Found : C, 52·7; H, 4·6; N,

[14] Perkin and Plant, *J.*, 1924, **125**, 1503.

13·1%). The *acetyl derivative* was a colourless syrup, b. p. 150° (bath-temp.)/0·001 mm., $\lambda_{max.}$ 252, 291 mμ (ε 11,500, 6500) (Found: C, 73·2; H, 7·7; N, 5·4%).

1 : 2 : 3 : 4 : 10 : 11-Hexahydro-8-methoxycarbazole, b. p. 94—96°/0·01 mm., crystallised in the refrigerator, and a sample pressed on porous tile had m. p. 29°. After purification through the hydriodide and distillation, the base melted sharply at 31° and had $\lambda_{max.}$ 245, 288 mμ (ε 7600, 2300). The *hydriodide*, precipitated by the addition of aqueous potassium iodide to a solution of the base in dilute acetic acid, formed prisms, m. p. 210—211°, from water, and needles, m. p. 211—212° from ethanol–ether (Found: C, 47·2; H, 5·5; N, 4·2. $C_{13}H_{17}ON,HI$ requires C, 47·1; H, 5·5; N, 4·2%). The picrate forms stout yellow prisms, m. p. 152—153° (decomp.), from methanol (Found: N, 13·0%). The *acetyl derivative* was a colourless gum, b. p. 140—150° (bath-temp.)/0·001 mm., $\lambda_{max.}$ 217·5, 256 mμ (ε 32,300, 12,600) (Found: C, 73·2; H, 7·9; N, 5·8%).

Degradation of 9-*Acetyl*-1 : 2 : 3 : 4 : 10 : 11-*hexahydro*-7-*methoxycarbazole*.—A solution of the acetyl compound (1·35 g.) in acetic acid (5 ml.) was slowly added to a mixture of nitric acid (21 ml.; *d* 1·42), acetic acid (5 ml.), and acetic anhydride (5 ml.) at −5°. After 1 hr. at −5° to 0°, the mixture was poured on ice and made alkaline with aqueous ammonia. The brown, amorphous product (1·6 g.) was suspended in water (200 ml.) at 70°, and 2% aqueous potassium permanganate (36 equivs.) was added with stirring during 2 hr., the temperature being gradually raised to 100°. After a further hour, the manganese dioxide was removed; after ignition it weighed 3·6 g., corresponding to the utilisation of 16·5 atomic proportions of oxygen. The filtered solution was acidified and the excess of permanganate was reduced with sulphur dioxide. The liquor was extracted with ether (2 × 150 ml.), and the material extracted was separated into acidic and non-acidic fractions. The former, a partly crystalline paste (167 mg.), was triturated with ether, and the undissolved pale yellow solid (32 mg.), m. p. 220—223° with previous sintering, was purified by sublimation in a vacuum followed by crystallisation twice from aqueous acetone; it then had m. p. 229—233°, undepressed by admixture with material, m. p. 229—234°, obtained by nitration of 2-acetamido-4-methoxybenzoic acid with nitric acid in acetic anhydride at 0°.

Concentration of the aqueous liquor to a small volume, followed by extraction with ether, gave an acidic fraction from which a small amount of adipic acid, m. p. and mixed m. p. 145—148°, was isolated.

Nitroaspidospermine.—Nitric acid (2 ml.; *d* 1·42; free from nitrous acid) was added with shaking to a solution of aspidospermine (1·01 g.) in glacial acetic acid (2 ml.) containing urea (50 mg.) at 40—45° during 10 min. After being heated at 45—50° for 30 min., the red mixture was poured on ice, basified with concentrated aqueous ammonia, and well extracted with ether. The ether-extracted material crystallised from methanol in two crops, both of m. p. 147—148° (0·943 g., 83%); the mother-liquor yielded an intractable red resin. Pure *nitroaspidospermine* separates from ethanol as pale yellow prisms, m. p. 149—149·5° (Found: C, 66·3; H, 7·3; N, 11·1; Ac, 10·1. $C_{22}H_{29}O_4N_3$ requires C, 66·1; H, 7·2; N, 10·5; Ac, 10·8%). This compound is recovered unchanged after 3 minutes' refluxing in acetic anhydride containing a trace of sulphuric acid.

Deacetylnitroaspidospermine.—Nitroaspidospermine (0·127 g.) was refluxed in 20% aqueous toluene-*p*-sulphonic acid for 2 hr. and the deep orange-red solution was worked up for basic material. This was obtained as an orange solid which crystallised from aqueous methanol in two crops, m. p. 144—146° (99 mg.) and m. p. 143—145° (5 mg.) (yield 91%). Pure *deacetylnitroaspidospermine* separates from aqueous methanol as deep yellow, pointed blades, m. p. 144—146° (Found: C, 66·7; H, 7·3; N, 11·8. $C_{20}H_{27}O_3N_3$ requires C, 67·2; H, 7·5; N, 11·7%).

Permanganate Oxidation of Nitroaspidospermine.—A well-stirred solution of pure nitroaspidospermine (1·11 g.) in stabilised acetone (50 ml.) was gradually treated with aqueous 0·7% barium permanganate (10 equivs.) at room temperature; the oxidising agent was used up 1 hr. after completion of the addition. Distilled water was added (100 ml.), and most of the acetone was boiled off on a boiling-water bath. Addition of barium permanganate was then continued at 100° until the solution remained pink after 1½ hr. at 100°. Altogether 39 atomic proportions of oxygen were used up.

The reaction mixture was filtered hot, the manganese dioxide was digested twice with 50 ml. of boiling distilled water for 1 hr., and the combined filtrates were treated with a little methanol to reduce the last traces of permanganate and then concentrated to small bulk *in vacuo*. A

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small quantity of manganese dioxide was filtered off, and the yellow solution (30 ml.) was basified with barium hydroxide solution and extracted thrice with ether; the neutral and basic material thus obtained weighed 1·5 mg.

The aqueous layer was rendered acid to Congo-red with dilute sulphuric acid and extracted with ether (5 × 50 ml.); the combined extracts yielded a brownish-yellow resin (169 mg.) which partially crystallised under a little methanol as needles. After a few hours, this crystalline solid (23 mg.) was collected as an off-white material, sintering at 140° and becoming glassy at 152—160°. The mother-liquor failed to yield further crystalline material. The crystalline acid was recrystallised from methanol–acetone, very small colourless needles (14 mg.) being obtained (m. p. 159·5—161° without flowing); a further crystallisation changed the m. p. behaviour to a marked sintering from 150°, the substance clearing, but not flowing, at 160° (Found: C, 55·6; H, 5·9; N, 7·9. $C_{17}H_{22}O_7N_2$ requires C, 55·7; H, 6·0; N, 7·6%).

We thank the Department of Scientific and Industrial Research for Maintenance Awards (to J. R. C. and G. F. S.). We are grateful to Dr. A. J. Everett for numerous absorption-spectrum measurements, and to Mr. P. R. W. Baker for some of the microanalyses.

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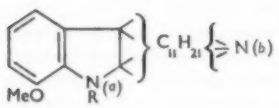
221. *The Constitution of Aspidospermine. Part III.* Reactivity at the Nitrogen Atoms, and Biogenetic Considerations.*

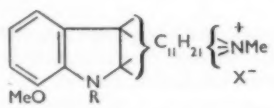
By A. J. EVERETT, H. T. OPENSHAW, and G. F. SMITH.

Aspidospermine methiodide and deacetyl-*N*-methylaspidospermine dimethiodide have been prepared, and the nature of deacetyl-*N*-methylaspidospermine monomethiodide has been established. Thermodynamic dissociation constants of aspidospermine and several derivatives are recorded. A tentative structure for aspidospermine is discussed from the biogenetic aspect.

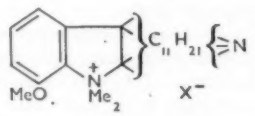
ASPIDOSPERMINE (Ia) does not react with methyl iodide at room temperature,[1] and previous attempts to prepare a methiodide at elevated temperature have resulted only in ill-defined, amorphous products. However, a crystalline methiodide (IIa) has now been obtained by prolonged interaction of the components at 56°. The rather sluggish reactivity of the basic nitrogen atom, N(*b*), is most probably due to steric hindrance, since its basic strength (see Table) is comparable with that of strychnine, for example, which reacts readily with methyl iodide.



(I) a: R = Ac
b: R = H
c: R = Me



(II) a: R = Ac, X = I
b: R = Me, X = I
c: R = H, X = Br



(III) a: X = I
b: X = Br

Deacetylaspidospermine (Ib), in contrast, reacts with methyl iodide in the cold to give deacetyl-*N*(*a*)-methylaspidospermine monomethiodide hydriodide (this product was wrongly described by Ewins[1] as a dimethiodide[2,3]). On treatment with alkali this gives the monomethiodide, which Witkop and Patrick[3] designated as deacetyl-*N*(*a*)-methylaspidospermine *N*(*b*)-methiodide (IIb) without any clear justification. In view of the

* Part II, preceding paper.

[1] Ewins, *J.*, 1914, **105**, 2738.
[2] Openshaw, Smith, and Chalmers, 13th Internat. Congr. Pure & Appl. Chem., 1955, Abs., p. 223.
[3] Witkop and Patrick, *J. Amer. Chem. Soc.*, 1954, **76**, 5603.

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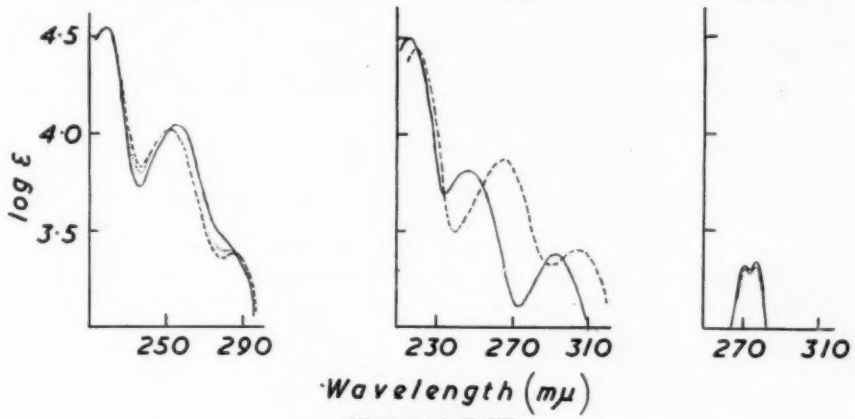
low reactivity of $N(b)$ in aspidospermine, the structure (IIIa) seemed to us more probable, and this is shown to be correct by a comparison of the ultraviolet absorption spectra of various aspidospermine derivatives. In agreement with expectation, Fig. 1 shows that protonation or quaternisation of $N(b)$ does not fundamentally alter the spectrum of aspidospermine. In contrast, the profound effect of protonation of $N(a)$ is shown by comparing the spectra of deacetylaspidospermine (Fig. 2) and its dihydrochloride (Fig. 3). Since the spectrum of deacetyl-$N(a)$-methylaspidospermine monomethobromide (derived from the

FIG. 1. FIG. 2. FIG. 3.



All spectra in EtOH.

FIG. 1. *Absorption spectra of aspidospermine* (——), *aspidospermine in* 0·1N-HCl (. . . .), *and aspidospermine methiodide* (– – – –).

FIG. 2. *Absorption spectra of deacetylaspidospermine* (——) *and deacetyl-*N(a)*-methylaspidospermine* (– – – –).

FIG. 3. *Absorption spectra of deacetyl-*N(a)*-methylaspidospermine* N(a)*-methobromide* (——) *and deacetylaspidospermine in* 0·1N-HCl.

methiodide) resembles that of deacetylaspidospermine dihydrochloride (Fig. 3), the structure (IIIa) is established for the monomethiodide.

The correctness of structure (IIIa) is confirmed by a consideration of the pK_a values of

pK_a *Values of aspidospermine and derivatives in aqueous solution.*

Compound	Basic centre	pK_a at 25°	Method
Aspidospermine (Ia)	$N(b)$	7·63, 7·51	1, 2
Deacetylaspidospermine (Ib)	$N(b)$	8·45, 8·48	1, 2
	$N(a)$	2·70	3
Deacetylaspidospermine $N(b)$-methobromide (IIc)	$N(a)$	2·60 *	4
Deacetyl-$N(a)$-methylaspidospermine $N(a)$-methobromide (IIIb)	$N(b)$	6·13	1, 3
Hexahydro-8-methoxycarbazole	$N(a)$	5·43	4
Strychnine	$N(b)$	8·26	1

1, Titration in dilute solution (10^{-4}—10^{-5}M). 2, Precipitation titration. 3, Titration (10^{-1} and 10^{-2}M). 4, Spectroscopic. * At 21°.

The thermodynamic pK_a values were obtained by applying a correction, according to the Debye–Hückel equation, to pK_a' values derived from measurements in dilute aqueous solution. Deacetylaspidospermine $N(b)$-methobromide was titrated at ionic strengths ranging from 2×10^{-5} to 2×10^{-3} and the extrapolated pK_a was identical within the limits of measurement ($\pm$ 0·01 pK_a unit) with the values corrected according to the above method. Details of the experimental techniques will be published later.

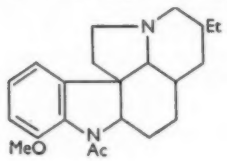
the compounds shown in the Table. The dissociation constant of the related methobromide (IIIb) corresponds to that of non-quaternised $N(b)$ in the environment of the positive charge on $N(a)$. By contrast, deacetylaspidospermine $N(b)$-monomethobromide

(IIc), prepared by the hydrolysis of aspidospermine methiodide, has a dissociation constant corresponding to the second dissociation constant of deacetylaspidospermine.

The difference between the pK_a of $N(a)$ in (IIc), or in deacetylaspidospermine, and the pK_a of hexahydro-8-methoxycarbazole ($\Delta pK_a = 2{\cdot}73$ and $2{\cdot}63$ respectively) can be attributed to the influence of the positive charge on $N(b)$. The effect on the pK_a of $N(b)$ of a positive charge on $N(a)$ is similar but somewhat smaller [compare (IIIb) with (Ib); $\Delta pK_a = 2{\cdot}32$]. Presumably this is because the positive charge on $N(a)$ is delocalised through polarisation of the attached methoxylated benzene ring.* Comparison of these pK_a differences with those recorded [4, 5] for the diamines, $H_2N{\cdot}[CH_2]_n{\cdot}NH_2$ ($n = 2$, $\Delta pK_a = 3{\cdot}0$; $n = 3$, $\Delta pK_a = 2{\cdot}0$), suggests that $N(a)$ and $N(b)$ in aspidospermine are separated by 2 or 3 carbon atoms. The greater compactness and rigidity of the aspidospermine structure probably increases the ΔpK_a value over that for an open-chain diamine, and the observed values are thus consistent with a separation of the nitrogen atoms by a chain of 3 carbon atoms.

The monomethiodide (IIIa) does not react with methyl iodide in the cold, but does so readily at 100°, giving deacetyl-$N(a)$-methylaspidospermine dimethiodide. Preliminary observations indicate that both this compound and aspidospermine methiodide (IIa) are susceptible to Hofmann degradation; in contrast, and in agreement with the assigned structure, the quaternary hydroxide derived from the monomethiodide (IIIa) does not undergo ring-fission but gives deacetyl-$N(a)$-methylaspidospermine (Ic) on pyrolysis.[2, 3]

Failure to dehydrogenate aspidospermine or its derivatives to indole derivatives by



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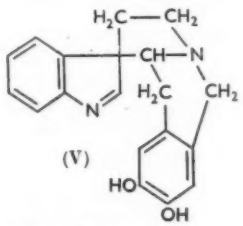

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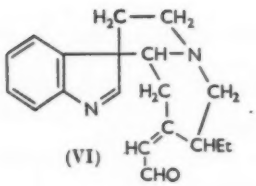

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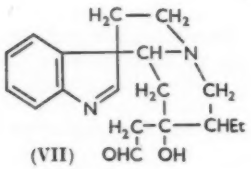

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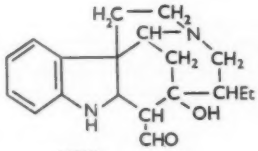
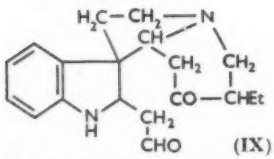
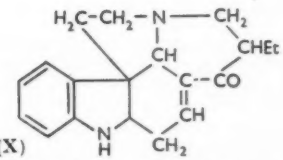


(VIII)



(IX)



(X)

means of mild oxidising agents such as mercuric acetate indicates the presence of a blocked dihydroindole structure, and suggests that aspidospermine belongs biogenetically to the "β-indole series." [6] The structure (IV) has been proposed [2, 3, 7] because it accounts well

* The pK_a of $N(b)$ in aspidospermine is lowered similarly, but to a lesser extent, by the influence of the dipolar $CH_3{\cdot}CO{\cdot}N(a)$ group.

[4] Rometsch, Marxer, and Miescher, *Helv. Chim. Acta*, 1951, **35**, 1611.
[5] Schwarzenbach and Epprecht, *ibid.*, 1936, **19**, 169.
[6] Robinson, "The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955, p. 119.
[7] Smith, Ph.D. Thesis, St. Andrews, 1949.

for the formation of 3-ethylindole and 3 : 5-diethylpyridine on distillation with zinc dust,[8] but it was not at first apparent how such a structure could be reconciled with Woodward's biogenetic scheme.[9] If, however, the supposed biogenetic intermediate (V) is assumed to be converted into (VI), hydration of the αβ-unsaturated carbonyl system could lead to (VII) which [unlike (VI)] could undergo the typical cyclisation to (VIII). By a reversal of an aldol condensation, (VIII) may then suffer ring-opening to (IX), which by cyclisation involving the keto-methylene group gives the desired skeleton (X).

It is difficult to envisage any other series of processes which would provide the required 3 : 5-diethylpyridine moiety. The presence of a *C*-ethyl group in aspidospermine has been confirmed by the application of Bickel, Schmid, and Karrer's [10] modification of the Kuhn–Roth method.

Experimental

Aspidospermine Methiodide (IIa).—Aspidospermine (481 mg.) and methyl iodide (5 ml.) were heated in a sealed tube at the b. p. of acetone (56°) for 4 days. The pure product (632 mg., 95%) which crystallised was collected and washed with a little ethanol. *Aspidospermine methiodide* crystallised from ethanol as colourless prisms which decomposed with complete volatilisation between 280° and 290°, $\lambda_{max.}$ 254, 285 mμ (ε 10,800, 3200 respectively) (Found : C, 55·45; H, 6·75; N, 5·85. $C_{23}H_{33}O_2N_2I$ requires C, 55·65; H, 6·7; N, 5·65%). At 300°/0·01 mm. the methiodide (25·3 mg.) decomposed to give almost pure aspidospermine, m. p. 207—210°, in the form of a sublimate (18·6 mg. Calc. for loss of CH_3I : 18·2 mg.).

Deacetyl-N(a)-*methylaspidospermine* N(a)-*Methobromide* (IIIb).—A solution of deacetyl-*N*(*a*)-methylaspidospermine *N*(*a*)-methiodide (IIIa) (1·40 g.) in water (150 ml.) was shaken with excess of freshly precipitated silver oxide for 6 hr. in the dark. The clear halogen-free filtrate was treated with 0·76N-hydrobromic acid (5·0 ml.), concentrated *in vacuo* to a small volume, treated with aqueous sodium carbonate, and extracted with chloroform. Evaporation of the chloroform solution yielded the pure crystalline methobromide (1·18 g.). One crystallisation from benzene–ethanol yielded analytically pure *deacetyl*-N(a)-*methylaspidospermine* N(a)-*methobromide*, $\lambda_{max.}$ 271, 278 mμ (ε 2070, 2120), which decomposed with evolution of methyl bromide at about 170° depending on the rate of heating (Found, in air-dried product : C, 61·15, 61·3; H, 7·7, 7·8; N, 6·2, 6·45; Br, 18·5. $C_{22}H_{33}ON_2Br,\frac{1}{2}H_2O$ requires C, 61·35; H, 7·95; N, 6·5; Br, 18·55%).

The methobromide (51·1 mg.) was heated to melting at 180°, kept at that temperature for 1 min., and the tube then evacuated to 10 mm. for 1 min. The residue was completely soluble in light petroleum and weighed 39·9 mg. (Calc. for loss of $CH_3Br,\frac{1}{2}H_2O$: 38·8 mg.).

Deacetyl-N(a)-*methylaspidospermine Dimethiodide* (with J. R. Chalmers).—Deacetyl-*N*(*a*)-methylaspidospermine monomethiodide (IIIa) (370 mg.) in methyl iodide (3 ml.) was heated in a sealed tube at 100° for 2 hr. The *dimethiodide* (420 mg., 87%) which had crystallised was collected, washed with anhydrous ether, and dried; it had m. p. 195—196° (Found : C, 45·3; H, 6·2; I, 42·6. $C_{23}H_{36}O_2N_2I$ requires C, 45·3; H, 5·9; I, 41·6%). Recrystallisation from moist acetone gave the monohydrate, m. p. 172°, which was not dehydrated at 100° over phosphoric oxide in a vacuum (Found : C, 43·7; H, 5·9; N, 4·3. $C_{23}H_{36}O_2N_2I_2,H_2O$ requires C, 43·9; H, 6·0; N, 4·5%).

Deacetylaspidospermine N(b)-*Methobromide Hydrobromide*. (IIc)—Aspidospermine methiodide (800 mg.) was shaken with a suspension of excess of silver oxide in water (70 ml.), and the filtered iodide-free solution was concentrated under reduced pressure, and treated with pure 5N-hydrobromic acid (50 ml.). The solution was heated to 100° in an evacuated sealed tube for 7 hr., then evaporated to dryness under reduced pressure. The residual colourless gum of deacetylaspidospermine *N*(*b*)-methobromide hydrobromide (812 mg.) did not crystallise. The derived deacetylaspidospermine *N*(*b*)-methobromide (IIc), $\lambda_{max.}$ 248, 292 mμ (ε 6450, 2200), was also amorphous.

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The Wellcome Research Laboratories, Beckenham, Kent. [*Received, October 26th*, 1956.]

[8] Witkop, *J. Amer. Chem. Soc.*, 1948, **70**, 3712.
[9] Woodward, *Nature*, 1948, **162**, 155.
[10] Bickel, Schmid, and Karrer, *Helv. Chim. Acta*, 1955, **38**, 649.

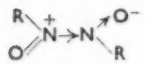
XUM

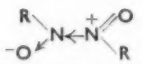
222. *The Structures and Stabilities of the Dimeric Forms of Nitroso-compounds.*

By J. W. Smith.

The molecular polarisation and molecular refraction of the more stable form of dimeric nitrosomethane, as determined from measurements on dilute solutions in benzene, differ only by 7·5 c.c. This difference is much smaller than would be expected for a structure which permits rotation about a N–N bond. If, however, the N–N linkage is assumed to have essentially a double-bond character, and the dimer studied is the *trans*-form, the result can be interpreted in terms of a fairly high atom polarisation, the major contribution to which arises from the bending of the polar N–O bonds. A reason for the different stabilities of the dimeric forms of various nitroso-compounds is suggested.

The structures of the dimeric forms of organic nitroso-compounds have been a subject of speculation. From the chemical properties, and particularly the *ortho-para*-directing character of the group in the dimeric forms of aromatic nitroso-compounds, Hammick, New, and Sutton [1, 2] inferred in 1932 that they were best represented by a form of resonance state frequently suggested at that time and involving, in this case, high-frequency alternation between structures (I) and (II). Of the other possibilities, structure (III) was rejected as being inadmissible on chemical evidence, and structures (IV) and (V) were rejected as suggesting too stable a molecule.


(I)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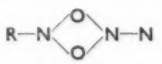
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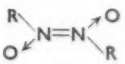
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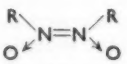
(V)

In carbon tetrachloride solution at 0° the dissociation of the dimeric form of 2 : 5-dimethyl-2-nitrosohexane is slow. Hence Hammick, New, and Williams [2] were able to study the change of the dielectric constants of these solutions with time, and thence to derive the values at zero time. From the results so obtained they inferred that the dipole moment of the dimeric form was about 1 D. Similarly, from measurements on benzene solutions containing the known equilibrium proportions of monomer and dimer, they obtained a value of about 1·5 D for the moment of the dimeric form of nitrosomesitylene. They interpreted these results as supporting the structure they proposed, since the molecule would be expected to have a small moment due to rotation about the central N–N bond out of the *trans*-configuration which the molecule would tend to assume owing to the repulsion of similar dipoles.

In interpreting the results of their measurements on nitrosomesitylene solutions, however, Hammick, New, and Williams assumed that the difference between the molecular polarisations of nitrosobenzene and the monomeric form of nitrosomesitylene is equal to the difference between the values for nitrobenzene and nitromesitylene. They therefore made the tacit assumption that the difference between the dipole moments of nitrosobenzene and the monomeric form of nitrosomesitylene is much greater than the difference between the moments of nitrobenzene and nitromesitylene. This is not justified, and it is noticeable that their values for the molecular polarisation of the dimeric form of nitrosomesitylene are least for the solutions in which the ratio of dimer to monomer is greatest, so the true moment of the dimeric form is probably much smaller than the value they derived.

[1] Hammick, *J.*, 1931, 3105; Hammick, New, and Sutton, *J.*, 1932, 742.
[2] Hammick, New, and Williams, *J.*, 1934, 29.

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The determination of the dipole moment of a compound from measurements on solutions containing other polar molecules is always rather uncertain, especially when the concentration of other polar molecules changes with the concentration of the species under consideration. Until recently, however, no stable dimeric nitroso-compound was available for study, but it has now been shown by Gowenlock and Trotman [3] that dimeric nitrosomethane exists in two fairly stable forms. By analogy with the azo- and azoxy-compounds they suggest that these are the geometrical isomers (IV) and (V), the more stable dimer *A* being the *trans*-form. This view is supported by both chemical and spectroscopic evidence.

It appears to be impossible to measure the dipole moments of both forms by the dilute solution method, as the less stable dimer *B* passes rapidly into dimer *A* in the non-polar solvents which are suitable for these measurements. However a small sample of dimer *A* was kindly placed at the author's disposal by Dr. B. G. Gowenlock, and the results of measurements on its solutions in benzene are shown in the table, where α, β, and γ are the mean values of $d\varepsilon/dw$, dv/dw, and dn^2/dw, respectively, and the remaining symbols have their usual significance.

Polarisation data for the dimer A *of nitrosomethane in benzene solution at* 25°.

$100w$	0·0000	0·4791	0·8237	1·1690
ε	2·2741	2·2759	2·2774	2·2790
v	1·14460	1·14296	1·14180	1·14063
n_D	1·4980	1·4980	1·4980	1·4980

$\alpha = 0{\cdot}40_4$, $\beta = 0{\cdot}340$, $\gamma = 0{\cdot}00$; whence $P_{2\infty} = 28{\cdot}7$ c.c., $[R_D]_2 = 21{\cdot}2$ c.c.

If the difference between $P_{2\infty}$ and $[R_\infty]_2$ were to be interpreted as arising from a permanent dipole moment, the value of the latter would be 0·61 D. A *trans*-form of the dimer, as in (IV), should have zero moment, whilst the *cis*-form, as in (V), would be expected to have a moment at least as great as that of *cis*-azoxybenzene [4] (4·68 D). Any structure which permits even a restricted rotation about the N–N bond should lead to a moment much in excess of 0·6 D. The evidence suggests, therefore, that the molecule is essentially rigid and symmetrical, with the oxygen, nitrogen, and carbon atoms all in one plane.

If each nitrogen atom is linked to the other, and to one of the oxygen atoms, by σ-bonds, there remain six electrons (one from each oxygen atom and two from each nitrogen atom) for π-bond formation. Ignoring the hyperconjugative effect of the methyl groups, and assuming the O–N and N–N resonance integrals to be each equal to β, L.C.A.O. treatment indicates that if the coulombic integrals of the nitrogen and oxygen atoms are taken as equal ($\alpha_O = \alpha_N$) the mobile bond orders of the N–O and N–N bonds are 0·448 and 0·725, respectively. Alternatively, if α_O is taken as $\alpha_N + \beta$, the mobile bond orders are 0·354 and 0·927, respectively. It also indicates that the formal charges on the oxygen and nitrogen atom are −0·725 and +0·725, respectively, when $\alpha_O = \alpha_N$, and −0·853 and +0·853, respectively, when $\alpha_O = \alpha_N + \beta$.

These calculations indicate that the mobile bond order of the N–N bond is the greater the smaller is the electronegativity of the nitrogen atoms. In the dimeric forms of nitrosomethane the hyperconjugative effect of the methyl groups will tend to increase the π-electron density in the O–N–N–O system and effectively to decrease the electronegativity of the nitrogen atoms, thus increasing the double-bond character of the N–N linkage and increasing its stability. In the dimeric forms of nitrosobenzene, on the other hand, conjugation with the phenyl groups will have exactly the reverse effects and so weaken the N–N bond. This may account for the facts that the dimeric form of nitrosobenzene is very unstable, and that the greatest stability of the dimeric form is encountered when the

[3] Gowenlock and Trotman, *J.*, 1955, 4190.
[4] Gehrckens and Müller, *Annalen*, 1933, **500**, 296.

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nitroso-group is linked to a primary carbon atom, where hyperconjugative effects are greatest.[5] It is also pertinent that the most stable dimer of an aromatic nitroso-compound appears to be that of nitrosomesitylene, where steric effects restrict its conjugation with the O–N–N–O system.

If, therefore, the stable dimer *A* of nitrosomethane has essentially the structure (IV), the molecule contains two fairly large opposed dipoles, so a rather large atom polarisation is to be expected. Hence it seems most probable that the $P_{2\infty} - [R_D]_2$ difference of 7·5 c.c. should be attributed to this cause. Since the N–O bonds have some double-bond character, the main contribution to the atom polarisation will probably arise from bending vibrations of these bonds in the C–N=N–C plane. Bond stretching and probably also the out-of-plane bending will be associated with much higher force constants, and hence their contributions will be only small. Hence, as a first approximation, the whole of the atom polarisation can be attributed to in-plane bending, and the system regarded as two one-dimensional oscillators. The expression for the atom polarisation then becomes ${}_AP = 8\pi N^2\mu^2{}_1/9k_b$, where μ_1 is the effective moment of the N–O bond, and k_b is the in-plane bending force constant in erg/radian^2. As in all similar instances it is difficult to estimate the effective value of μ_1. It is unsafe to use the result of the molecular-orbital calculation quoted above, since this method tends to exaggerate the charge distribution. The value is likely to be larger than the moment of *trans*-azoxybenzene [4] (1·705 D), since in the latter compound the true N–O bond moment is partly compensated by the lone-pair moment at the second nitrogen atom. When it is assumed that the $P_{2\infty} - [R_D]_2$ difference represents the whole of the atom polarisation, and a value of $\mu_1 = 1{\cdot}7$ D is used, it follows that $k_b = 6{\cdot}4 \times 10^{-13}$ erg/radian^2, whilst the more probable value of $\mu_1 = 2{\cdot}2$ D leads to $k_b = 10{\cdot}7 \times 10^{-13}$ erg/radian^2. The latter value compares closely with the figure of 12×10^{-13} erg/radian^2 for the bending of the two C=O bonds in the plane of the ring in benzoquinone, a figure based on an ${}_AP$ value [6] of 8·8 c.c. and an effective bond moment of 2·5 D. This value of the force constant for benzoquinone predicts an absorption band at 113 cm.$^{-1}$, very close to the value of 120 cm.$^{-1}$ observed by Cartwright and Errera,[7] thus indicating that the treatment of each C=O bond as a one-dimensional oscillator is reasonable. The double-bond character of the N–O bonds is probably less than that of the C–O bonds, but nevertheless the behaviours are likely to be closely parallel. In the present instance the frequency predicted by a force constant of $10{\cdot}7 \times 10^{-13}$ erg/radian^2 corresponds with an absorption band at about 100 cm.$^{-1}$, but no measurements extending so far into the infra-red region have been recorded.

Thanks are offered to Dr. B. G. Gowenlock for his gift of the sample of dimer, and to Imperial Chemical Industries Limited for the loan of a precision condenser and a grant for purchase of materials.

Bedford College, Regent's Park, London, N.W.1. [*Received, October* 31*st*, 1956.]

[5] Gowenlock and Trotman, *J.*, 1956, 1670.
[6] Hammick, Hampson, and Jenkins, *J.*, 1938, 1263; Boud and Smith, *J.*, 1956, 4507.
[7] Cartwright and Errera, *Proc. Roy. Soc.*, 1936, *A*, **154**, 138.

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223. *Addition of Methyl Radicals to Substituted Benzenes.*

By W. J. Heilman, A. Rembaum, and M. Szwarc.

Methyl affinities of some substituted benzenes were determined at 65°. It was found that the addition of methyl radicals to substituted benzenes is slightly accelerated by F, Cl, and Br atoms, and retarded by the OCH_3 group. Methyl affinities of *p*- and *m*-dichlorobenzenes are nearly identical and higher than that of the monochloro-derivative.

The rates of addition are also enhanced by CN, OAc, and CO_2Et groups. An exceptionally high reactivity of nitrosobenzene is probably due to the reaction of methyl radicals with the nitroso-group. One has to distinguish, therefore, between the effect of a substituent upon the reactivity of the benzene ring, and the effect due to the addition reaction involving a substituent (*e.g.*, the addition of a radical to styrene).

The results now reported are compared with Hey's results on the rate of phenylation. The trends in both reactions are very similar.

The work of Hey and his co-workers [1-3] on the effect of substituents upon the rate of phenylation of benzene derivatives induced us to study similar reactions involving, however, methyl instead of phenyl radicals. In the system studied by Hey, a compound, generating phenyl radicals by its decomposition, is dissolved in an equimolecular mixture of two aromatic solvents, say HA_1 and HA_2. Under the conditions of Hey's experiments, the decomposition yields eventually the phenylated solvent molecules, A_1Ph and A_2Ph, and it is the purpose of the experiment to determine their mole ratio.

In the interpretation of his results Hey assumes tacitly that the phenyl radicals, generated in his system, are added to the respective aromatic compounds according to equation (1):

$$Ph + A{\cdot}H \longrightarrow Ph{\cdot}A{\cdot}H \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The radicals formed in reaction (1) are supposed to react rapidly with radicals R according to equation (2):

$$Ph{\cdot}A{\cdot}H{\cdot} + R \longrightarrow Ph{\cdot}A + RH \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

and thus to yield the final product of the reaction. If reaction (2) is much faster than reaction (1), *i.e.*, if reaction (1) is rate-determining in the overall phenylation process, and if radicals R participating in reaction (2) are different from Ph·A·H radicals, then the molar ratio $PhA_1 : PhA_2$ gives the ratio of the bimolecular rate constants of reactions (1) for A_1H and A_2H respectively.

This scheme seems to be plausible. It appears that the Ph·CO·O radicals are fulfilling the rôle of R radicals when benzoyl peroxide is used for generating phenyl radicals, since the equivalent amount of benzoic acid is formed in the process. Furthermore, Hey demonstrated [4] that the ratio $PhA_1 : PhA_2$ is approximately independent of the nature of the compound used for generating phenyl radicals. To complete the evidence in favour of the suggested scheme it would be desirable, however, to measure the ratio $PhA_1 : PhA_2$ for a varying ratio $HA_1 : HA_2$ and to show the proportionality of these two variables; but, even in the absence of this information, Hey's results seem to be well founded.

A method was developed in our laboratories [5, 6] which permits one to determine the

[1] Augood, Hey, and Williams, *J.*, 1952, 2094; 1953, 44.
[2] Hey and Williams, *Discuss. Faraday Soc.*, 1953, **14**, 216.
[3] Cadogan, Hey, and Williams, *J.*, 1954, 794.
[4] Hey, Stirling, and Williams, *J.*, 1955, 3963.
[5] Levy and Szwarc, *J. Amer. Chem. Soc.*, 1955, **77**, 1949.
[6] Szwarc, *J. Polymer Sci.*, 1955, **16**, 367.

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relative rates of addition of methyl radicals to aromatic or olefinic compounds. The addition reaction is similar to reaction (1), namely,

$$CH_3 + HA \longrightarrow H{\cdot}A{\cdot}CH_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The kinetic basis of our technique was thoroughly investigated, and the method seems to be particularly useful when applied to reactive substrates. It is inferior, however, to Hey's method if one desires to determine the point of attack by a radical. While this information is easily obtained in Hey's method, unfortunately it is not available in our measurements.

The application of our technique to substituted benzenes is somewhat difficult since these compounds belong to the class of not too reactive substrates. This forces us to work with very high mole-fractions of substrates, and consequently we have to change considerably the environment in which the reaction proceeds. The results are, therefore, not as good as desirable although the conclusions are very definite. We confirm the essential findings of Hey, namely, that the effect of a substituent on the rate of addition of radicals is small as compared with the enormous effects observed in reactions involving ionic intermediates. However, the addition of methyl radicals seems to be more affected by a substituent than the addition of phenyl radicals. We find also that fluorinated, chlorinated, and brominated benzenes are more reactive than benzene, which parallels Hey's findings on the rate of phenylation. Furthermore, nitrobenzene seems to be more reactive than benzene. However, the latter reactions show some pecularities which probably indicate the reversibility of the addition process, *e.g.*, $CH_3{\cdot}C_6H_5{\cdot}NO_2 \rightleftharpoons C_6H_5{\cdot}NO_2 + CH_3{\cdot}$. These results are omitted, therefore, from the present paper and will be discussed later. On the other hand, we found that anisole is less reactive than benzene. This result parallels that obtained in a series of quinones,[7] and we believe that it illustrates the general rule that electron-donating groups slow down the radical addition, while electron-withdrawing groups accelerate it.* However, the phenomenon is more complex if one deals with substituents which are themselves unsaturated. A possible explanation of these phenomena is given in a paper by Szwarc.[8] It is noteworthy that a deactivation effect of the *tert.*-butyl group was found by Cadogan, Hey, and Williams [9] and attributed to steric hindrance.

All the experimental results are listed in Table 1, while the relative rate constants of addition of methyl radicals to the substituted benzenes are listed in Table 2. The latter values are referred to as methyl affinities, and a value of unity has been arbitrarily chosen for the methyl affinity of benzene.

Experimental

The experimental technique has been described fully.[5,6,10] Methyl radicals were generated by thermal decomposition of dilute solutions of acetyl peroxide in 2-methylheptane. The amounts of methane and carbon dioxide formed were determined quantitatively. On addition of the desired amount of aromatic or olefinic compounds the amount of methane formed decreases, and it is assumed that the decrease is due to reaction (3). Hence, the relative rate constant of reaction (3) could be determined from the relative decrease in the amount of methane formed.

Commercial reagents were used, purified as usual if necessary. Their purity was checked by their b. p.s or m. p.s.

All the experiments were carried out at 65° in 2-methylheptane. The concentration of acetyl peroxide was of the order 3×10^{-2}M, and about 6% of the peroxide was decomposed in

* This conclusion is based on some, as yet unpublished, results. The generalization should be taken cautiously since methyl or ethyl groups exhibit, sometimes, an effect contrary to their electron-donating power. See ref. 8 and Buckley and Szwarc, *J. Amer. Chem. Soc.*, 1956, **78**, 5696.

[7] Rembaum and Szwarc, *J. Amer. Chem. Soc.*, 1955, **77**, 4468.
[8] Szwarc, *J. Phys. Chem.*, in the press.
[9] Cadogan, Hey, and Williams, *J.*, 1954, 3352.
[10] Leavitt, Levy, Szwarc, and Stannett, *J. Amer. Chem. Soc.*, 1955, **77**, 5493.

each experiment. The second column of Table 1 gives the mole % of substrate in the solution; the next two columns give the amounts of carbon dioxide and methane formed in the reaction. These two values give the $CH_4 : CO_2$ ratio used in calculating k_3/k_1. The $CH_4 : CO_2$ ratio obtained in pure 2-methylheptane was determined to be 0·800. k_3 denotes the rate constant of the addition reaction (3), while k_1 denotes the rate constant of hydrogen abstraction from 2-methylheptane. Finally, the last column in Table 1 gives the unimolecular rate constant of the decomposition of acetyl peroxide measured by the amount of carbon dioxide formed.

Discussion

The k_3/k_1 values for benzene had been determined by Levy and Szwarc.[5] The present results at 65° (0·22 and 0·24) compare well with theirs, namely 0·26, 0·33, and 0·29. However, in order to preserve the self-consistency of the present data we have chosen the average of our two determinations as our standard value used in the calculation of methyl affinities.

Table 1 shows that the relative rates of addition of methyl radicals are approximately independent of the concentration of the investigated substrates, although in the case of fluorobenzene and benzonitrile the data reveal a definite trend. The change in the molar

Table 1.

Compound	Mole %	$CO_2 \times 10^2$ (millimoles)	$CH_4 \times 10^2$ (millimoles)	k_3/k_1	$10^5 k_u$ (sec.$^{-1}$)
C_6H_6	50	0·480	0·315	0·22	0·89
,,	50	0·483	0·310	0·24	0·90
PhOMe	75	0·794	0·460	0·13	2·10
,,	75	0·818	0·430	0·18	2·16
PhF	25	0·415	0·275	0·62	1·02
,,	50	0·398	0·215	0·48	1·01
,,	50	0·433	0·230	0·51	1·10
,,	75	0·370	0·132	0·38	1·02
PhCl	25	0·382	0·230	0·98	0·96
,,	25	0·354	0·210	1·05	0·89
,,	50	0·351	0·150	0·87	0·89
,,	50	0·355	0·145	0·95	0·90
PhBr	50	0·355	0·153	0·86	0·90
,,	50	0·350	0·156	0·80	0·89
p-$C_6H_4Cl_2$	25	0·352	0·150	2·7	0·89
m-$C_6H_4Cl_2$	25	0·388	0·162	2·8	0·88
PhCN	10	0·398	0·260	2·0	0·82
,,	10	0·404	0·260	2·2	0·89
,,	25	0·459	0·190	2·8	0·95
,,	25	0·465	0·190	2·9	0·99
,,	50	0·515	0·088	3·7	1·08
,,	50	0·495	0·096	3·1	1·04
Ph·COMe	75	0·690	0·204	0·57	1·62
,,	75	0·665	0·204	0·54	1·58
Ph·CO_2Et	25	0·456	0·252	1·3	0·96
,,	25	0·445	0·250	1·3	0·93
,,	50	0·450	0·170	1·1	0·93

Table 2. *Methyl affinities of substituted benzenes at* 65°.

Compound	Methyl affinity	Compound	Methyl affinity
Benzene	1·0	Anisole	0·65 ± 0·15
Fluorobenzene	2·2 ± 0·2	Benzonitrile	12·2 ± 1·5
Chlorobenzene	4·2 ± 0·2	Acetophenone	2·4
Bromobenzene	3·6 ± 0·2	Ethyl benzoate	5·2
p-Dichlorobenzene	11·7	Nitrosobenzene	10^5
m-Dichlorobenzene	12·2		

ratio 2-methylheptane : substrate by a factor of 9 (from 3 to 1/3) changes the relative rate of methyl-radical addition to fluorobenzene by less than a factor of 2, a similar change in the ratio affects the rate of addition to benzonitrile by only 50%. Although we do not know the detailed reasons for such trends, we suspect that they are caused by a considerable

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change of the environment in which the reaction proceeds, which in turn leads to second-order effects in the kinetics. It is noteworthy that the increase in the concentration of substrates decreases the apparent reactivity of fluorobenzene but increases that of benzonitrile.

The last column of Table 1 gives the rate constant k_u of the decomposition of acetyl peroxide. It is important that this rate constant remains essentially unaffected by the presence of substrate,* indicating that the substrate does not react directly with the peroxide. The only exceptions are anisole and, to a smaller extent, acetophenone. While the rate of decomposition seems to be twice as high in 75 mole % of anisole as in pure 2-methylheptane solution, the increase in the rate amounts only to about 50% in the case of acetophenone. These effects are not surprising since it is known that ethers accelerate the rate of decomposition of peroxides.[11, 12]

The results obtained for chloro- or bromo-benzene might be vitiated by the abstraction reaction, *e.g.*, $C_6H_5Br + CH_3 \longrightarrow C_6H_5 + CH_3Br$. In our method of calculation of k_3/k_i such a reaction would increase the apparent value of k_3/k_i. Qualitative tests † seem to indicate, however, that methyl chloride is not formed in the reaction, and that the amount of methyl bromide formed is negligible.

Comparison of Hey's results with ours, summarised in Table 2, indicates a greater spread in the reactivities of substituted benzenes towards methyl radicals than towards phenyl radicals. Since our work was carried out at 65° while Hey's was at 80°, the difference in reactivities should be greater in our investigation. Moreover, one has to realise that the ratio of reactivities of various substrates depends not only on their nature but also on the nature of the attacking radical (see the discussion of intrinsic reactivities of radicals in refs. 4—7). Hey and Williams [2] discuss the relative reactivities in terms of changes in localization energies. They assume that the change in the latter is *equal* to the change in the activation energy of the process, while all that could be expected is a proportionality between the difference in activation energies and the difference in the respective localisation energies.

Finally, we discuss the reactivity of nitrosobenzene. Two experiments were carried out with this compound one with 0·1 mole % solution in 2-methylheptane, and the other with the same concentration of nitrosobenzene in ethyl methyl ketone: k_3/k_i was calculated from the first experiment at 29,000, while k_3/k_{EMK} was calculated from the second experiment at about 3000. Since, $k_{EMK} = 9k_i$ (see ref. 9), the result of the second experiment can be recalculated into the k_3/k_i scale to give a value of about 27,000. Thus, the agreement between these two results is satisfactory.

It is obvious that the high value of methyl affinity of nitrosobenzene does not result from the activation of the benzene ring, but it represents a reaction between a methyl radical and the nitroso-group. Hence, in discussing reactions of substituted benzene, one has to distinguish between the effect of a substituent upon the reactivity of the benzene ring and an effect resulting from a reaction taking place on the substituent. For example, the high methyl affinity of styrene is not caused by the activation of the benzene ring by the vinyl group but by the " activation " of a molecule of ethylene by the phenyl group.

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* The rate constant of the unimolecular decomposition of acetyl peroxide at 65° and in pure 2-methylheptane solution is $0{\cdot}95 \times 10^{-5}$ sec.$^{-1}$.

† These tests were performed by adding a few drops of the reacting solution to a methanolic solution of silver nitrate.

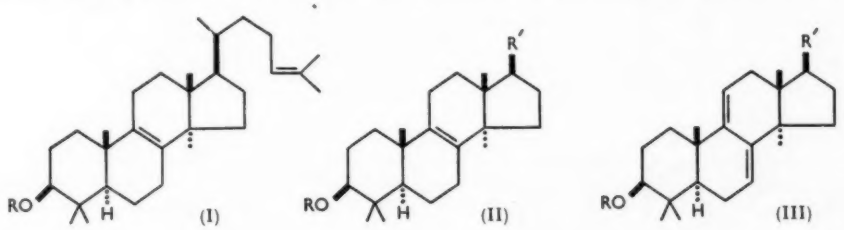
[11] Nozaki and Bartlett, *J. Amer. Chem. Soc.*, 1946, **68**, 1686.
[12] Smid, Rembaum, and Szwarc, *ibid.*, 1956, **78**, 3315.

224. *The Synthesis of Lanosterol (Lanostadienol).*

By (*a*) R. B. Woodward and A. A. Patchett, and
(*b*) D. H. R. Barton, D. A. J. Ives, and R. B. Kelly.

Cholesterol has been converted in a series of steps (*a*) into 14-methylcholestanol, identical with material obtained earlier from lanostenol, and (*b*) into lanostenol. By further processes the latter has been transformed into lanosterol (lanosta-8 : 24-dienol) and agnosterol [lanosta-7 : 9(11) : 24-trienol]. These changes, coupled with the already known conversion of lanostenol into γ-lanosterol [lanosta-7 : 9(11)-dienol], represent total syntheses of all four wool-fat triterpenoids.

The triterpenoid fraction of wool fat consists of four alcohols : lanosterol (lanosta-8 : 24-dienol) (I; R = H) and lanostenol (II; R = H, R′ = C_8H_{17}) which are present in major amount, and agnosterol [lanosta-7 : 9(11) : 24-trienol] (III; R = H, R′ = C_8H_{15}) and γ-lanosterol [lanosta-7 : 9(11)-dienol] (III; R = H, R′ = C_8H_{17}) which are present in minor amount.[1] The constitutions of these compounds have been established by degradation [2] and by *X*-ray crystallography.[3] The relative stereochemistry was also established in the latter investigations as well as by chemical [4] and biochemical [5] considerations. The absolute stereochemistry, already proposed from molecular-rotation arguments,[6] was also supported by these biochemical considerations. We now report (for preliminary communications see ref. 7) the conversion of cholesterol into all four wool-fat triterpenoids. This work not only provides an unambiguous confirmation for



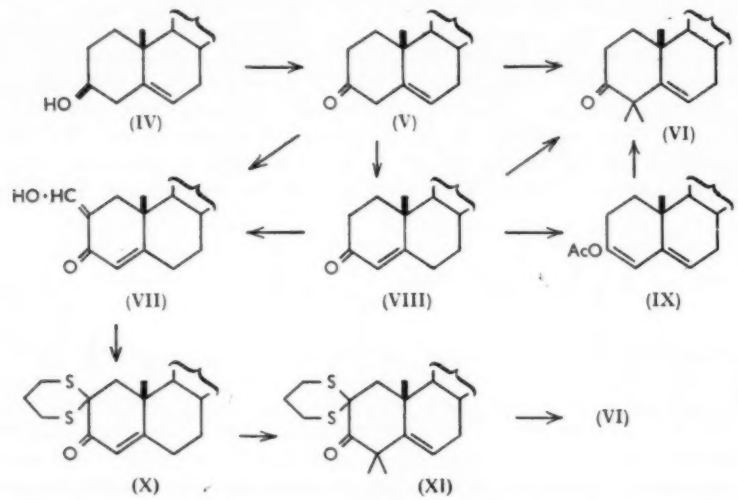
all the conclusions summarised in the references cited above but, having regard to the total syntheses of cholesterol already effected,[8] also constitutes a total synthesis of all four wool-fat triterpenoids.[9]

We consider first the introduction of the *gem.*-dimethyl grouping into ring A of cholesterol (IV). Cholesterol can be readily converted through cholest-5-en-3-one (V) and cholest-4-en-3-one (VIII) (for rapid and convenient procedures for the preparation of

[1] For summary, see Elsevier's " Encyclopaedia of Organic Chemistry," Vol. 14 and supplement.
[2] Voser, Mijovic, Heusser, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 2414, and many earlier papers; Cavalla, McGhie, and Pradhan, *J.*, 1951, 3142, and earlier papers; Barnes, Barton, Cole, Fawcett, and Thomas, *J.*, 1953, 571, and earlier papers.
[3] Curtis, Fridrichsons, and Mathieson, *Nature*, 1952, **170**, 321; Fridrichsons and Mathieson, *J.*, 1953, 2159.
[4] Barnes, Barton, Fawcett, and Thomas, *J.*, 1953, 576.
[5] Kyburz, Riniker, Schenk, Heusser, and Jeger, *Helv. Chim. Acta*, 1953, **36**, 1891; Woodward and Bloch, *J. Amer. Chem. Soc.*, 1953, **75**, 2023.
[6] Klyne, *J.*, 1952, 2916.
[7] Woodward, Patchett, Barton, Ives, and Kelly, *J. Amer. Chem. Soc.*, 1954, **76**, 2852; Barton, Ives, Kelly, Woodward, and Patchett, *Chem. and Ind.*, 1954, 605.
[8] Woodward, Sondheimer, and Taub, *J. Amer. Chem. Soc.*, 1951, **73**, 3548; Woodward, Sondheimer, Taub, Heusler, and McLamore, *ibid.*, 1952, **74**, 4223; Cardwell, Cornforth, Duff, Holtermann, and Robinson, *J.*, 1953, 361.
[9] Cf. Halsall and Thomas, *J.*, 1956, 2431.

these ketones see ref. 10) into the enol acetate [11] (IX). Treatment of the acetate with potassium amide and methyl iodide in liquid ammonia [12] afforded, albeit in poor yield, 4 : 4-dimethylcholestenone (VI). An alternative methylation procedure using potassium *tert.*-butoxide and methyl iodide (see below) gave a much superior yield of the desired ketone (VI).

The methods of synthesis of (VI) indicated above do not, within the limits of microanalysis, define its constitution unambiguously. A proof of constitution was achieved by the following stepwise synthesis. Cholest-4-en-3-one (VIII) was converted into its hydroxymethylene derivative [13] (VII), and the latter treated with the ditoluene-*p*-sulphonate of propane-1 : 3-dithiol in the presence of potassium acetate, a procedure developed by one of us (R. B. W.) in collaboration with Dr. Irwin Pachter, to give the dithioketal (X). Methylation of this compound with potassium *tert.*-butoxide and methyl iodide furnished (XI), the constitution of which is defined by the absence of an αβ-unsaturated ketone band in the ultraviolet spectrum. Removal of the dithioketal protecting grouping with Raney nickel gave 4 : 4-dimethylcholestenone (VI) of defined constitution.

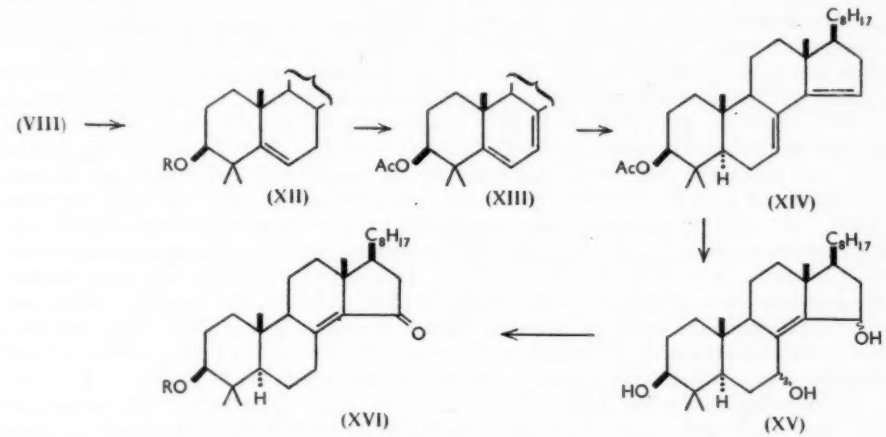


The most convenient synthesis of the ketone (VI) was finally realised in direct methylation of the precursors (V) or (VIII) by potassium *tert.*-butoxide and methyl iodide under carefully defined conditions. The yield from either ketone was in excess of 60%.

In order to effect methylation at $C_{(14)}$ along the lines developed above for methylation at $C_{(4)}$, it was conceived that the 15-oxo-$\Delta^{8(14)}$-system would constitute a suitable intermediate, especially as a convenient route to such compounds had been reported.[14] The desired 3β-hydroxy-4 : 4-dimethylcholest-8(14)-en-15-one (XVI; R = H) was obtained in the following way. Reduction of 4 : 4-dimethylcholestenone (VI) with lithium aluminium hydride gave 4 : 4-dimethylcholesterol (XII; R = H), characterised as its acetate (XII; R = Ac). Treatment of the latter with *N*-bromosuccinimide in carbon tetrachloride solution and then with collidine [15] afforded 7-dehydro-4 : 4-dimethylcholesteryl

[10] Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 5421.
[11] Westphal, *Ber.*, 1937, **70**, 2128.
[12] Cf. Birch, Quartey, and Smith, *J.*, 1952, 1768, and references there cited.
[13] Burr, Holton, and Webb, *J. Amer. Chem. Soc.*, 1950, **72**, 4903.
[14] Barnes, Barton, and Laws, *Chem. and Ind.*, 1953, 616; Barton and Laws, *J.*, 1954, 52.
[15] Cf. Bide, Henbest, Jones, Peevers, and Wilkinson, *J.*, 1948, 1783; Buisman, Stevens, and Vliet, *Rec. Trav. chim.*, 1947, **66**, 83; Redel and Gauthier, *Bull. Soc. chim. France*, 1948, 607; Antonucci, Bernstein, Littell, Sax, and Williams, *J. Org. Chem.*, 1952, **17**, 1341.

acetate (XIII). The constitution of the latter acetate was established by its ultraviolet absorption spectrum [$\lambda_{max.}$ 273 and 282 mμ (ε = 11,200 and 11,000 respectively)], its strong negative rotation ([α]$_D$ − 107°), and its mode of preparation. Treatment of this acetate with hydrogen chloride in chloroform at −40° and then with anhydrous ammonia in methanol at −60° furnished 4 : 4-dimethylcholesta-7 : 14-dienyl acetate (XIV), the constitution of which is established by analogy [16] and by its further reactions (see below). Reaction of this with perphthalic acid, followed by saponification, gave a triol which, from analogy,[14] is formulated as 4 : 4-dimethylcholest-8(14)-ene-3β : 7ξ : 15ξ-triol (XV). This triol was very insoluble in chloroform, which fact greatly facilitated its purification. Its dehydration with ethanolic hydrochloric acid gave the desired 3β-hydroxy-4 : 4-dimethylcholest-8(14)-en-15-one (XVI; R = H), characterised as the derived benzoate.



Whilst these experiments were in hand parallel studies on the methylation of the 15-oxo-$\Delta^{8(14)}$-system in known compounds were being prosecuted. Although treatment of 15-oxoergosta-8(14) : 22-dien-3β-yl acetate (XVII; R = Ac, R′ = C_9H_{17}) with only a slight excess of potassium *tert.*-butoxide and methyl iodide (conditions for preparing 4 : 4-dimethylcholestenone : see above) gave unchanged starting material, methylation by means of a very large excess of the *tert.*-butoxide (approx. 50 mols.) and methyl iodide (approx. 70 mols.) afforded 3β-methoxy-14-methylergosta-7 : 22-dien-15-one (XVIII; R = Me, R′ = C_9H_{17}) in moderate yield. This compound showed infrared maxima (in CCl_4 solution) at 1738 (*cyclo*pentanone), 1104 (C–O–C of methyl ether), 962 (*trans*-CH=CH– in side chain) and 1410 cm.$^{-1}$ (CH_2·CO in five-membered ring) in agreement with the assigned constitution. By chromatography of the reaction product 14-methyl-15-oxoergosta-7 : 22-dien-3β-yl acetate (XVIII; R = Ac, R′ = C_9H_{17}), characterised by hydrolysis to the corresponding alcohol (XVIII; R = H, R′ = C_9H_{17}), could also be isolated. The acetate was, however, the minor product of the reaction. The 15-oxo-grouping in these compounds was sterically hindered and could not be removed by Wolff–Kishner reduction under ordinary conditions. Thus attempted reduction of the ether (XVIII; R = Me, R′ = C_9H_{17}) gave only the corresponding alcohol (XIX; R = Me, R′ = C_9H_{17}, R″ = H) which was characterised as the acetate (XIX; R = Me, R′ = C_9H_{17}, R″ = Ac). The configuration of the hydroxyl group is regarded as probably α on the basis of conformational (see ref. 14) and molecular-rotation (see ref. 17) considerations. However, application of the modified Wolff–Kishner reduction conditions

[16] Cf. Barton and Brooks, *J.*, 1951, 277.
[17] Klyne and Stokes, *J.*, 1954, 1979.

of Barton, Ives, and Thomas,[18] which are specially suited for the reduction of hindered ketones, afforded without difficulty 3β-methoxy-14-methylergosta-7 : 22-diene (XX; R = Me, R′ = C_9H_{17}), characterised by hydrogenation over palladised calcium carbonate to 3β-methoxy-14-methylergost-7-ene (XX; R = Me, R′ = C_9H_{19}). The assignment of the nuclear ethylenic linkage to the 7(8)- rather than 8(9)-position in these and related compounds (see below) was based originally on molecular-rotation considerations. The assignment is, however, rigidly established by further transformations outlined in the sequel.

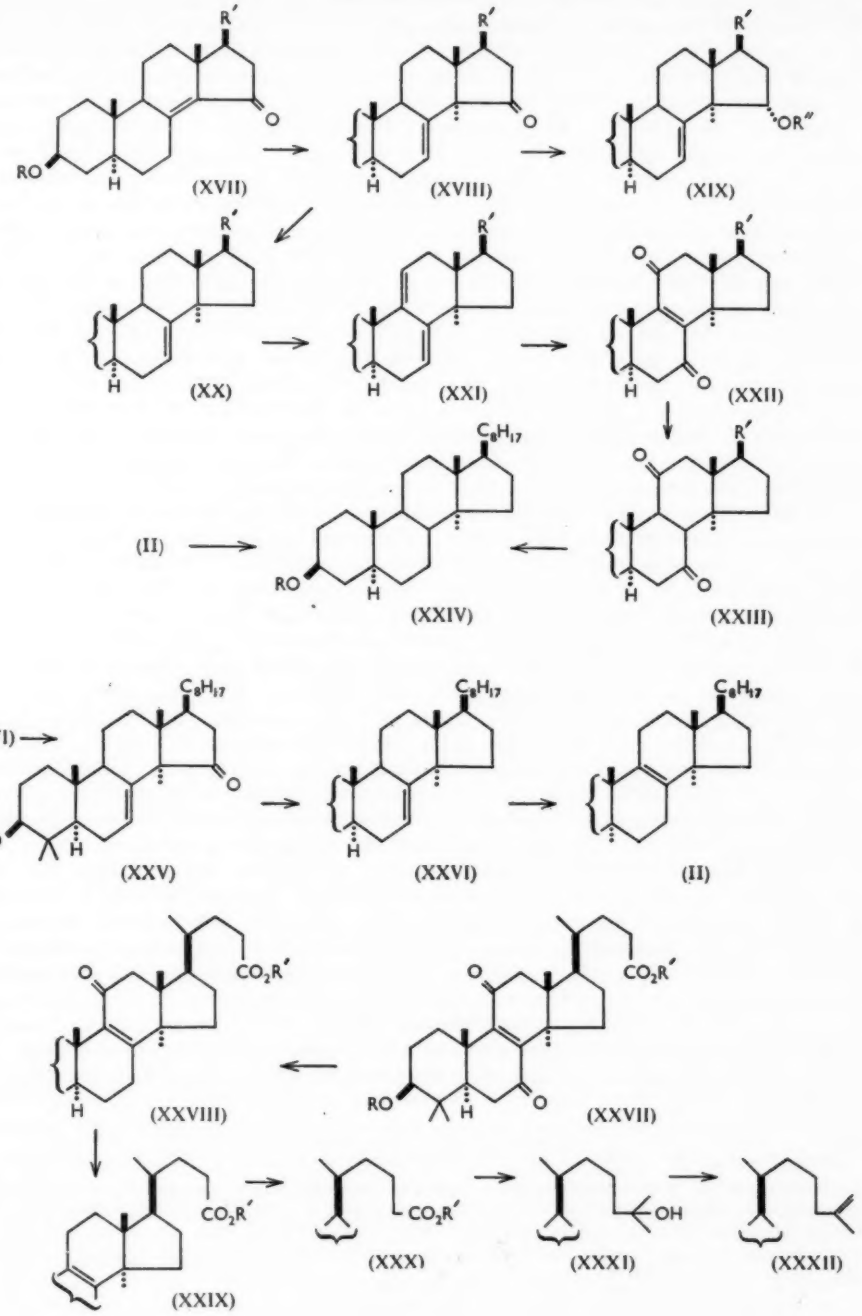
Under analogous conditions 15-oxocholest-8(14)-en-3β-yl acetate (XVII; R = Ac, R′ = C_8H_{17}) was converted into 3β-methoxy-14-methylcholest-7-en-15-one (XVIII; R = Me, R′ = C_8H_{17}) and thence into 3β-methoxy-14-methylcholest-7-ene.

Although the desired methylation at $C_{(14)}$ had been effected in the above-mentioned compounds, the concomitant methylation at $C_{(3)}$ precluded any direct comparison with lanostenol derivatives. In order to protect the 3-hydroxyl group, methylation of the appropriate benzoates was investigated. Methylation of 15-oxoergosta-8(14) : 22-dien-3β-yl benzoate (XVII; R = Bz, R′ = C_9H_{17}), prepared essentially according to the method of Barton and Laws,[14] gave 14-methyl-15-oxoergosta-7 : 22-dien-3β-yl benzoate (XVIII; R = Bz, R′ = C_9H_{17}) which was smoothly reduced by the modified Wolff–Kishner method to 14-methylergosta-7 : 22-dien-3β-ol (XX; R = H, R′ = C_9H_{17}). The way was now clear for direct inter-relation of cholesterol and lanostenol through the known 14-methylcholestanol.[19] To this end 15-oxocholest-8(14)-en-3β-yl benzoate (XVII; R = Bz, R′ = C_8H_{17}) was methylated to give 14-methyl-15-oxocholest-7-en-3β-yl benzoate, reduction of which afforded, after rebenzoylation, 14-methylcholest-7-en-3β-yl benzoate (XX; R = Bz, R′ = C_8H_{17}). In a second reduction the crude product was acetylated to give the corresponding acetate (XX; R = Ac, R′ = C_8H_{17}). Oxidation of 14-methylcholest-7-en-3β-yl benzoate (XX; R = Bz, R′ = C_8H_{17}) with selenium dioxide afforded the derived 7 : 9(11)-diene (XXI; R = Bz, R′ = C_8H_{17}) which, without isolation, was oxidised further with chromium trioxide to furnish 14-methyl-7 : 11-dioxocholest-8-en-3β-yl benzoate (XXII; R = Bz, R′ = C_8H_{17}). Treatment of this compound with zinc dust and acetic acid gave 14-methyl-7 : 11-dioxocholestan-3β-yl benzoate (XXIII; R = Bz, R′ = C_8H_{17}), further reduced by the modified Wolff–Kishner method [18] to give, after rebenzoylation, 14-methylcholestan-3β-yl benzoate (XXIV; R = Bz), identical with a specimen prepared by benzoylation of the known 14-methylcholestanol obtained by degradation of lanostenol.[19] The identity was confirmed by comparison of the appropriate alcohols (XXIV; R = H) and acetates (XXIV; R = Ac).

With these preliminaries completed we return to the direct route from cholesterol to lanostenol. Methylation of 4 : 4-dimethyl-15-oxocholest-8(14)-en-3β-yl benzoate (XVI; R = Bz) (see above) gave the expected 4 : 4 : 14-trimethyl-15-oxocholest-7-en-3β-yl benzoate (XXV; R = Bz), which was reduced by the modified Wolff–Kishner method [18] to lanost-7-enol (XXVI; R = H).[20] The identity was established by a detailed comparison of the alcohols and of the derived acetates. Lanost-7-enol, in which the position of the ethylenic linkage has been rigidly established,[21] was then converted into its benzoate which, on treatment with hydrogen chloride in chloroform, gave, on careful chromatography, some lanostenyl benzoate (II; R = Bz). The identity of the latter was established by direct comparison and also by hydrolysis to lanostenol (II; R = H) and conversion of this into its acetate (II; R = Ac). The oxidation of lanostenol to γ-lanosterol (dihydroagnosterol) (III; R = H, R′ = C_8H_{17}) has been reported on many previous occasions.[1]

With the successful completion of the synthesis of the two wool-fat triterpenoids with saturated side chains, attention was directed to the conversion of lanostenol (II; R = H, R′ = C_8H_{17}) into lanosterol (II; R = H) and agnosterol (III; R = H, R′ = C_8H_{15}).

[18] Barton, Ives, and Thomas, *J.*, 1955, 2056.
[19] *Idem*, *J.*, 1954, 903.
[20] Marker, Wittle, and Mixon, *J. Amer. Chem. Soc.*, 1937, **59**, 1368.
[21] Cavalla, McGhie, and Pradhan, *J.*, 1951, 3142; Barton, Fawcett, and Thomas, *J.*, 1951, 3147.


(XVII)
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Vigorous oxidation of lanosteryl acetate with chromic acid gave, although in poor yield, the known 7 : 11-dioxotrisnorlanostenoloic acid acetate (XXVII; R = Ac, R′ = H), giving on hydrolysis the alcohol (XXVII; R = R′ = H) and by methylation the acetate methyl ester (XXVII; R = Ac, R′ = Me). The compounds of this series are more conveniently available by chromic acid oxidation of suitable derivatives of technical "lanosterol" (see ref. 22). Wolff–Kishner reduction of methyl 7 : 11-dioxotrisnorlanostenoloate acetate (XXVII; R = Ac, R′ = Me) under Huang-Minlon conditions [23] furnished, after remethylation and reacetylation, methyl 11-oxotrisnorlanost-8-enoloate acetate (XXVIII; R = Ac, R′ = Me). Further Wolff–Kishner reduction of the latter under the modified conditions of Barton, Ives, and Thomas [18] afforded, after remethylation and reacetylation, methyl trisnorlanost-8-enoloate acetate (XXIX; R = Ac, R′ = Me). The two stage Wolff–Kishner reduction is essential since the application of the vigorous conditions of Barton, Ives, and Thomas [18] to 7 : 11-dioxolanostenyl acetate directly afforded only the *saturated* lanostanol. The position of the ethylenic linkage in the ester (XXIX; R = Ac, R′ = Me) was established by the fact that technical "lanosteryl acetate" could be ozonised at −60° in chloroform to afford, after further oxidation at room temperature with potassium permanganate, an acid fraction which on methylation furnished a methyl trisnorlanost-8-enoloate acetate of defined constitution and identical with that obtained by the Wolff–Kishner reduction technique outlined above. The ozonolysis procedure is, in fact, the more convenient preparative technique.

Of the various possible methods for building up again the lanosterol side chain the scheme summarised in the sequel seemed the most promising. Methyl trisnorlanost-8-en-oloate acetate was hydrolysed and then reacetylated to give trisnorlanost-8-enoloic acid acetate (XXIX; R = Ac, R′ = H). This was converted into the acid chloride by Wilds and Schunk's method [24] and this then subjected to Arndt–Eistert homologation in methanol solution, to give methyl bisnorlanost-8-enoloate acetate (XXX; R = Ac, R′ = Me). Reaction of the latter with an excess of the methyl Grignard reagent furnished, after reacetylation, 3β-acetoxylanost-8-en-25-ol (XXXI; R = Ac). Dehydration of this by heating it with fuller's earth in xylene afforded a crystalline mixture shown by its infrared band at 885 cm.$^{-1}$ to be rich in the *iso*propenyl compound (XXXII; R = Ac). With the limited amount of material available it was not possible to define acidic conditions which would isomerise the *iso*propenyl group to the desired *iso*propylidene form without at the same time tending to equilibrate the nuclear ethylenic linkage between positions 7(8) and 8(9). The difficulty was overcome in the following way.

Methyl 11-oxotrisnorlanost-8-enoloate acetate (XXVIII; R = Ac, R′ = Me) was homologated to methyl 11-oxobisnorlanost-8-enoloate acetate (XXXIII; R = Ac, R′ = Me) exactly as in the scheme outlined above. Reaction with excess of the methyl Grignard reagent followed by reacetylation then afforded 3β-acetoxy-11-oxolanost-8-en-25-ol (XXXIV; R = Ac). Treatment of this alcohol with dioxan–sulphuric acid at room temperature gave 11-oxolanosta-8 : 24-dienyl acetate (XXXV; R = Ac), and thence the alcohol (XXXV; R = H). Wolff–Kishner reduction of the acetate (XXXV; R = Ac) under the modified conditions [18] afforded, after reacetylation, lanosteryl acetate (I; R = Ac), identical with an authentic specimen kindly supplied by Dr. J. F. McGhie (Chelsea Polytechnic).

11-Oxolanosta-8 : 24-dien-3β-yl acetate was conveniently obtained from technical "lanosterol acetate" through the dibromide (XXXVII) * by chromic acid oxidation to

* We thank Dr. J. F. McGhie for his kindness in informing us of a convenient procedure for the preparation of this dibromide.[25] It is our understanding that Dr. McGhie and his colleagues have also obtained the diketone (XXXVIII) by a similar route to that described here.

[22] McGhie, Pradhan, Cavalla, and Knight, *Chem. and Ind.*, 1951, 1165; Voser, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 497.
[23] Huang-Minlon, *J. Amer. Chem. Soc.*, 1949, **71**, 3301.
[24] Wilds and Shunk, *J. Amer. Chem. Soc.*, 1950, **72**, 2388.
[25] Lewis and McGhie, *Chem. and Ind.*, 1956, 550.

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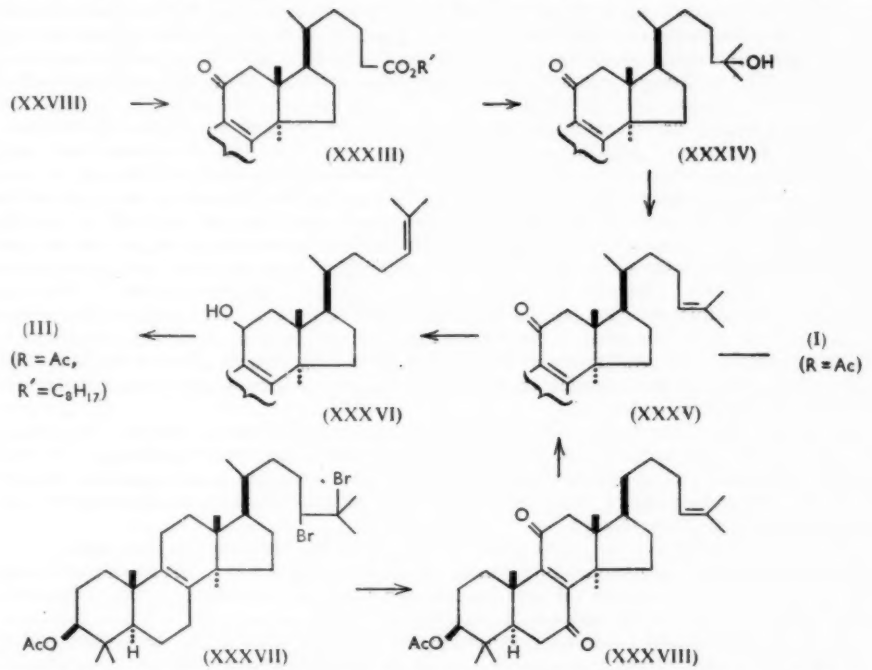
the corresponding 7 : 11-diketone, which with sodium iodide gave the diketone (XXXVIII). Selective Wolff–Kishner reduction, followed by reacetylation, then afforded the desired 11-oxolanosta-8 : 24-dien-3β-yl acetate (XXXV; R = Ac).

The synthesis of the fourth wool-fat triterpenoid, agnosterol, was also secured by using this oxo-acetate. Reduction with lithium aluminium hydride furnished lanosta-8 : 24-



diene-3β : 11β-diol (XXXVI), converted when heated with acetic anhydride and a trace of toluene-*p*-sulphonic acid into the required agnosteryl acetate (III; R = Ac, R′ = C_8H_{15}). A prior conversion of lanosterol into agnosterol does not appear to be recorded in the literature.

[*Added, January 12th*, 1957.—Dr. J. F. McGhie (Chelsea Polytechnic) has kindly informed us that, in collaboration with Dr. D. A. Lewis, he has also effected independently the conversion of lanosterol into agnosterol.]

Experimental

Rotations were determined in $CHCl_3$ solution, and ultraviolet absorption spectra in EtOH. Infrared spectra were determined either at Harvard or through the courtesy of Messrs. Glaxo Laboratories Ltd. Operations involving potassium *tert.*-butoxide were carried out under dry oxygen-free nitrogen.

4 : 4-*Dimethylcholest-5-en-3-one*.—(a) ***From* 3-*acetoxycholesta*-3 : 5-*diene*.** Potassium (1·54 g.) in liquid ammonia (500 ml.) was treated with a trace of ferric nitrate. When the blue colour had been discharged 3-acetoxycholesta-3 : 5-diene [11] (4·8 g.) in dry ether (40 ml.) was added. After 6 hours' stirring methyl iodide (4·0 ml.) was added. Two further additions of methyl iodide (17 ml. in all) were made during 45 min. The crude product in 95% ethanol (50 ml.) and concentrated hydrochloric acid (0·5 ml.) was refluxed for 20 min., then chromatographed over alumina (115 g.; Merck), to give mainly cholest-4-en-3-one with some **4 : 4-*dimethylcholest-5-en-3-one*** (200 mg.), m. p. (from ethanol) 176—177°, $[\alpha]_D$ +1° (*c* 2·19) (Found : C, 84·15; H, 11·9. $C_{29}H_{48}O$ requires C, 84·4; H, 11·7%).

The enol-acetate is more efficiently methylated by the following procedure. The enol-acetate (24·2 g., 0·0567 mole) in dry *tert.*-butyl alcohol (450 ml.) was treated with potassium (0·17 mole) in the same solvent (130 ml.). Then methyl iodide (21·2 ml.) in dry *tert.*-butyl alcohol (30 ml.) was at once admitted under nitrogen. After 10 min. the solution was refluxed for 1 hr. Filtration of the product over alumina in 2 : 1 light petroleum–benzene and crystallisation from chloroform–95% ethanol gave **4** : 4-dimethylcholest-5-en-3-one (13·9 g.).

(b) *From* 2 : 2-*trimethylenedithiocholest-4-en-3-one.* 2-Hydroxymethylenecholest-4-en-3-one[13] (1·5 g.) and propane-1 : 3-dithiol ditoluene-*p*-sulphonate (1·9 g.; kindly supplied by Dr. Irwin Pachter) in warm absolute ethanol (26 ml.) were treated with anhydrous potassium acetate (2·53 g.) in absolute ethanol (7 ml.) under reflux for 7 hr. Filtration of the product in benzene over alumina, and crystallisation from acetone, gave the *dithioketal*, m. p. 161—165° (1·18 g.). Further purification in the same way afforded a product, m. p. 179—180° (Found : C, 73·75; H, 9·95. $C_{30}H_{48}OS_2$ requires C, 73·7; H, 9·9%). The dithioketal (800 mg.), suspended in dry *tert.*-butyl alcohol (40 ml.), was treated with potassium (350 mg.) in *tert.*-butyl alcohol (5 ml.) under nitrogen with stirring. Methyl iodide (0·82 ml.) in dry butyl alcohol (10 ml.) was added. After 3 min. the temperature was raised from 40° to the b. p. and the mixture refluxed for 1 hr. Chromatography of the product over alumina (26 g.; Merck) gave 2 : 2-*trimethylenedithio*-**4** : 4-*dimethylcholest*-3-*one* (280 mg.). Recrystallised from acetone this had m. p. 178—179° (Found : C, 73·3; H, 9·9. $C_{32}H_{52}OS_2,Me_2CO$ requires C, 73·1; H, 10·15%). The dithioketal (103 mg.) in 95% ethanol (65 ml.) was refluxed for 6 hr. with Raney nickel (5 ml. of settled suspension; deactivated by refluxing for 3 hr. each with ethyl acetate and with acetone). Crystallisation of the product from 95% ethanol afforded **4** : 4-dimethylcholest-5-en-3-one (63 mg.) identical in m. p., mixed m. p., and infrared spectrum with material obtained as described under (a).

(c) *From cholest-4-en-3-one.* The ketone (9·58 g.) in dry *tert.*-butyl alcohol (160 ml.) at 40° was treated with a solution of potassium (2·92 g.) in the same solvent (60 ml.). At once methyl iodide (9·3 ml.) in dry *tert.*-butyl alcohol (10 ml.) was added and the mixture refluxed for 1 hr. Crystallisation of the product from chloroform–95% ethanol furnished **4** : 4-dimethylcholest-5-en-3-one (6·4 g.).

(d) *From cholest-5-en-3-one.* The ketone (79·6 g.) in dry *tert.*-butyl alcohol (1400 ml.) at 40° was treated with potassium (24·3 g.) in the same solvent (475 ml.). At once methyl iodide (77·5 ml.) was added and the mixture refluxed for 1 hr. Crystallisation of the product as above gave **4** : 4-dimethylcholest-5-en-3-one (53·8 g.).

4 : 4-*Dimethylcholesterol.*—**4** : 4-Dimethylcholest-5-en-3-one (33·0 g.) in dry ether (2·6 l.) was added to lithium aluminium hydride (6·06 g.) in the same solvent (575 ml.) with vigorous stirring during 45 min. (gentle reflux). Crystallisation of the product from ether–methanol gave **4** : 4-*dimethylcholesterol* (25 g.), m. p. 144—146°. Recrystallised for analysis this compound had m. p. 150—151°, $[\alpha]_D$ −64° (*c* 1·16) (Found : C, 83·6; H, 11·85. $C_{29}H_{50}O$ requires C, 84·0; H, 12·15%). Acetylation with pyridine–acetic anhydride on the steam-bath for 35 min. gave the derived *acetate*, m. p. (from chloroform–methanol) 136—137°, $[\alpha]_D$ −48° (*c* 2·15) (Found : C, 81·2; H, 11·35. $C_{31}H_{52}O_2$ requires C, 81·5; H, 11·5%).

7-*Dehydro*-**4** : 4-*dimethylcholesteryl Acetate.*—**4** : 4-Dimethylcholesteryl acetate (10·0 g.) in carbon tetrachloride (150 ml.) was treated with finely powdered *N*-bromosuccinimide (4·68 g.; added in one portion) with good stirring. A previously heated oil-bath held at 90—95° was raised up so that the carbon tetrachloride solution was totally immersed. At the same time illumination from a GE sun-lamp was directed into the reaction mixture. After 7½ min. a yellow-green colour developed and the reaction became exothermic. After a further 45 sec. the lamp was turned off and the hot oil-bath quickly replaced by a pan of ice and water. The time required for the exothermic reaction to begin is variable, but it is important that the start be recognised and the reaction stopped within a minute of its commencement.

With the ice-bath in position stirring was continued for a further 5 min. and the cold solution then filtered into redistilled collidine (20 ml.). The carbon tetrachloride was removed *in vacuo*, more collidine (5 ml.) added, and the reaction mixture heated on the steam-bath for 1½ hr. Dilution with light petroleum (b. p. 60—80°) precipitated collidine hydrobromide (4·21 g., 95%). Repeated filtration of the resulting yellow-brown solution through Hy-Flo removed most of the colour. After washing of the filtrate with 5% hydrochloric acid, and 5% aqueous sodium carbonate, and drying ($MgSO_4$), removal of the solvent *in vacuo* and crystallisation from ether–methanol gave 7-*dehydro*-**4** : 4-*dimethylcholesteryl acetate* (6·7 g., 67·5%). Recrystallised for

analysis from chloroform–methanol this had m. p. 151—152°, $[\alpha]_D$ −107° (*c* 1·27), $\lambda_{max.}$ 273 and 282 mμ (ε 11,200 and 11,000 respectively) (Found: C, 81·85; H, 11·0. $C_{31}H_{50}O_2$ requires C, 81·9; H, 11·1%).

4 : 4-*Dimethylcholesta*-7 : 14-*dien*-3β-*yl Acetate*.—7-Dehydro-4 : 4-dimethylcholesteryl acetate (3·0 g.) in chloroform (105 ml.) was treated with hydrogen chloride gas at −39° for 2 hr. The temperature was reduced to −60° and the hydrogen chloride neutralised by the addition of anhydrous ammonia in methanol at the same temperature. Crystallisation of the product from chloroform–methanol gave 4 : 4-*dimethylcholesta*-7 : 14-*dien*-3β-*yl acetate* (2·2 g.), m. p. 113—118°, $[\alpha]_D$ −136° (*c* 1·65). Recrystallisation changed the constants to m. p. 123—125°, $[\alpha]_D$ −132° (*c* 1·54), $\lambda_{max.}$ 244 mμ (ε 11,000) (Found: C, 82·2; H, 11·05. $C_{31}H_{50}O_2$ requires C, 81·9; H, 11·1%).

4 : 4-*Dimethylcholest*-8(14)-*ene*-3β : 7ξ : 15ξ-*triol*.—The mixture rich in 4 : 4-dimethylcholesta-7 : 14-dien-3β-yl acetate (see above) (3·0 g.) in anhydrous ether (150 ml.) was treated with monoperphthalic acid (1·372 g.) in the same solvent (24 ml.) at room temperature for 45 hr. The product (2·78 g.) in 95% ethanol (450 ml.) with potassium hydroxide (13 g.) was refluxed for 3 hr. and the ethanol removed *in vacuo*. After it had been washed with water, digestion of the product with chloroform (25 ml.) gave 4 : 4-*dimethylcholest*-8(14)-*ene*-3β-7ξ : 15ξ-*triol* (1·51 g.). Recrystallised from methanol this had m. p. 240—241° (Found: C, 77·75; H, 11·1. $C_{29}H_{50}O_3$ requires C, 77·95; H, 11·3%).

3β-*Hydroxy*-4 : 4-*dimethylcholest*-8(14)-*en*-15-*one*.—4 : 4-Dimethylcholest-8(14)-ene-3β : 7ξ : 15ξ-triol (1·51 g.), suspended in 95% ethanol (100 ml.) containing concentrated hydrochloric acid (5 ml.), was heated under reflux for 3 hr. Crystallisation of the product from aqueous ethanol gave 3β-*hydroxy*-4 : 4-*dimethylcholest*-8(14)-*en*-15-*one* (0·39 g.), m. p. 156—160°. Crystallisation from methanol afforded an analytical specimen of m. p. 161—162°, $[\alpha]_D$ +135° (*c* 1·44), $\lambda_{max.}$ 261 mμ (ε 14,700) (Found: C, 81·0; H, 11·1. $C_{29}H_{48}O_2$ requires C, 81·25; H, 11·3%). Treatment with pyridine–benzoyl chloride furnished the derived *benzoate*, m. p. (from 95% ethanol) 154—155°, $[\alpha]_D$ +137° (*c* 1·56), $\lambda_{max.}$ 232 and 260 mμ (ε 17,000 and 16,600 respectively) (Found: C, 80·85; H, 9·9. $C_{36}H_{52}O_3$ requires C, 81·15; H, 9·85%).

3β-*Hydroxy*-14-*methylergosta*-7 : 22-*dien*-15-*one and its Derivatives*.—To potassium (4·0 g.) in anhydrous *tert.*-butyl alcohol (70 ml.) there was added 15-oxoergosta-8(14) : 22-dien-3β-yl acetate [14] (500 mg.) in methyl iodide (10 ml.) in one portion. The solution was stirred at room temperature until neutral and the product reacetylated with pyridine–acetic anhydride on the steam-bath for 1 hr. Chromatography over alumina and elution with 1 : 1 light petroleum (b. p. 40—60°)–benzene gave 3β-*methoxy*-14-*methylergosta*-7 : 22-*dien*-15-*one*, m. p. (from methanol) 124—126°, $[\alpha]_D$ +31° (*c* 0·97) (Found: C, 81·85; H, 10·85. $C_{30}H_{48}O_2$ requires C, 81·75; H, 11·0%). Further elution with benzene afforded 14-*methyl*-15-*oxoergosta*-7 : 22-*dien*-3β-*yl acetate*, m. p. (from aqueous methanol) 150—152°, $[\alpha]_D$ +31° (*c* 1·31) (Found: C, 79·65; H, 10·15. $C_{31}H_{48}O_3$ requires C, 79·4; H, 10·3%). Alkaline hydrolysis furnished 3β-*hydroxy*-14-*methylergosta*-7 : 22-*dien*-15-*one*, m. p. (from aqueous methanol) 161—162°, $[\alpha]_D$ +34° (*c* 0·94) (Found: C, 81·2; H, 10·85. $C_{29}H_{46}O_2$ requires C, 81·65; H, 10·85%).

3β-*Methoxy*-14-*methylergosta*-7 : 22-*diene and its Derivatives*.—3β-Methoxy-14-methylergosta-7 : 22-dien-15-one (100 mg.) was heated in a sealed tube for 14 hr. at 180° with sodium (200 mg.) in absolute ethanol (2 ml.) and anhydrous hydrazine (0·5 ml.). Chromatography of the product over alumina and elution with ether gave 3β-*methoxy*-14-*methylergosta*-7 : 22-*dien*-15(?α)-*ol*, m. p. (from methanol) 109—110° (Found: C, 81·2; H, 11·35. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·35%). Acetylation with pyridine–acetic anhydride on the steam-bath for 1 hr. afforded the *acetate*, m. p. (from chloroform–methanol) 129—130°, $[\alpha]_D$ +14° (*c* 1·06) (Found: C, 79·45; H, 10·3. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%).

In contrast, Wolff–Kishner reduction of 3β-methoxy-14-methylergosta-7 : 22-dien-15-one by the procedure of Barton, Ives, and Thomas [18] for the preparation of lanostanol gave 3β-*methoxy*-14-*methylergosta*-7 : 22-*diene* (70%), m. p. (from methanol) 99—100°, $[\alpha]_D$ −24° (*c* 1·50) (Found: C, 84·1; H, 11·55. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%).

3β-Methoxy-14-methylergosta-7 : 22-diene (400 mg.) was hydrogenated in ethyl acetate solution in presence of palladised calcium carbonate. Crystallisation of the product from chloroform–methanol afforded 3β-*methoxy*-14-*methylergost*-7-*ene*, m. p. 88—89°, $[\alpha]_D$ −5° (*c* 1·54) (Found: C, 84·3; H, 11·8. $C_{30}H_{52}O$ requires C, 84·05; H, 12·2%).

3β-*Methoxy*-14-*methylcholest*-7-*en*-15-*one*.—To potassium (2·5 g.) in *tert.*-butyl alcohol (50 ml.) there was added 15-oxocholest-8(14)-en-3β-yl acetate (800 mg.) in methyl iodide (8 ml.)

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in one portion. The solution was stirred until neutral. Chromatography of the product over alumina and elution with benzene afforded 3β-*methoxy*-14-*methylcholest*-7-*en*-15-*one* (400 mg.), m. p. (from aqueous methanol) 86—87°, $[\alpha]_D$ +56° (*c* 0·92) (Found: C, 81·6; H, 11·2. $C_{29}H_{46}O_2$ requires C, 81·65; H, 10·85%). Wolff–Kishner reduction of this ketone as for the preparation of lanostanol [18] furnished 3β-*methoxy*-14-*methylcholest*-7-*ene* (80%), m. p. (from methanol) 66°, $[\alpha]_D$ +5° (*c* 1·66) (Found: C, 83·5; H, 12·0. $C_{29}H_{50}O$ requires C, 84·0; H, 12·15%).

14-*Methylergosta*-7 : 22-*dien*-3β-*ol and its Derivatives*.—Ergosta-7 : 14 : 22-trien-3β-yl benzoate (ergosterol B_3 benzoate) [16] (18·0 g.) was converted into 15-*oxoergosta*-8(14) : 22-*dien*-3β-*yl benzoate* (12·0 g.), m. p. (from ether–methanol) 175°, $[\alpha]_D$ +75° (*c* 1·50), $\lambda_{max.}$ 230 and 259 mμ (ε 21,100 and 16,800 respectively) (Found: C, 81·45; H, 9·45. $C_{35}H_{48}O_3$ requires C, 81·35; H, 9·35%), essentially by the method used by Barton and Laws [14] for the corresponding acetate but without separation into acid and neutral moieties.

To potassium (6·7 g.) in dry *tert.*-butyl alcohol (400 ml.) there was added 15-oxoergosta-8(14) : 22-dien-3β-yl benzoate (3·3 g.) in methyl iodide (35 ml.). The solution was stirred at room temperature until neutral (about 15 min.). Chromatography of the product over alumina (100 g.) and elution with mixtures of light petroleum (b. p. 40—60°) and benzene gave 14-*methyl*-15-*oxoergosta*-7 : 22-*dien*-3β-*yl benzoate* (1·2 g.), m. p. (from chloroform–methanol) 158—159°, $[\alpha]_D$ +36° (*c* 1·60), $\lambda_{max.}$ 229 mμ (ε 15,600) (Found: C, 81·05; H, 9·1. $C_{36}H_{50}O_3$ requires C, 81·45; H, 9·5%).

14-Methyl-15-oxoergosta-7 : 22-dien-3β-yl benzoate (500 mg.) was reduced by the Wolff–Kishner procedure as detailed by Barton, Ives, and Thomas [18] for the preparation of lanostanol. Crystallisation of the product from methanol gave 14-*methylergosta*-7 : 22-*dien*-3β-*ol* (300 mg., crude), m. p. 149—150°, $[\alpha]_D$ −15° (*c* 1·30) (Found: C, 84·1; H, 11·55. $C_{29}H_{48}O$ requires C, 84·4; H, 11·7%).

14-*Methylcholest*-7-*en*-3β-*yl Benzoate and its Derivatives*.—7-Dehydrocholesteryl benzoate (Messrs. Glaxo Laboratories Ltd.) (20 g.) was treated with hydrogen chloride gas as for the preparation of ergosta-7 : 14 : 22-trien-3β-yl benzoate.[16] The crude mixture of benzoates resulting after crystallisation from chloroform–methanol, was enriched in cholesta-7 : 14-dien-3β-yl benzoate {$[\alpha]_D$ −100° (*c* 1·67); (10 g.)}. This mixture was treated with perphthalic acid and the whole product further processed essentially according to the method of Barton and Laws.[14] The crude product (10 g.) was chromatographed over alumina. Elution with benzene gave 15-*oxocholest*-8(14)-*en*-3β-*yl benzoate* (3·8 g., pure), m. p. (from chloroform–methanol) 156°, $[\alpha]_D$ +103° (*c* 2·04), $\lambda_{max.}$ 230 and 258 mμ (ε 15,900 and 15,700 respectively) (Found: C, 80·7; H, 9·55. $C_{34}H_{48}O_3$ requires C, 80·9; H, 9·6%).

To potassium (5·0 g.) in dry *tert.*-butyl alcohol (250 ml.) there was added 15-oxocholest-8(14)-en-3β-yl benzoate (3·0 g.) in methyl iodide (30 ml.) in one portion. The solution was stirred until neutral. Chromatography of the product over alumina and elution with 1 : 1 light petroleum (b. p. 40—60°)–benzene afforded 14-*methyl*-15-*oxocholest*-7-*en*-3β-*yl benzoate* (670 mg.), m. p. (from chloroform–methanol) 145—147°, $[\alpha]_D$ +51° (*c* 0·50) (Found: C, 81·2; H, 9·75. $C_{35}H_{50}O_3$ requires C, 81·05; H, 9·7%).

14-Methyl-15-oxocholest-7-en-3β-yl benzoate (1·25 g.) was reduced by the Wolff–Kishner method as developed for the preparation of lanostanol.[18] The crude product was benzoylated with benzoyl chloride–pyridine and chromatographed over alumina. Elution with benzene afforded 14-*methylcholest*-7-*en*-3β-*yl benzoate* (750 mg.), m. p. (from chloroform–methanol) 174—176°, $[\alpha]_D$ +9° (*c* 1·20) (Found: C, 82·95; H, 10·4. $C_{35}H_{52}O_2$ requires C, 83·3; H, 10·4%). In a second experiment the crude alcohol was acetylated with pyridine–acetic anhydride to the *acetate*, m. p. (from chloroform–methanol) 95—96°, $[\alpha]_D$ +4° (*c* 1·19) (Found: C, 81·4; H, 11·15. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%).

14-*Methyl*-7 : 11-*dioxocholest*-8-*en*-3β-*yl Benzoate*.—14-Methylcholest-7-en-3β-yl benzoate (735 mg.) in glacial acetic acid (20 ml.) was refluxed with selenium dioxide (750 mg.) for 3 hr. The product, after filtration in benzene through a short column of alumina, was dissolved in glacial acetic acid (20 ml.) with addition of chromium trioxide (650 mg.) and heated at 90° for 2 hr. Chromatography of the neutral product over alumina and elution with benzene furnished 14-*methyl*-7 : 11-*dioxocholest*-8-*en*-3β-*yl benzoate* (280 mg.), m. p. (from chloroform–methanol) 180° (long needles), $[\alpha]_D$ +95° (*c* 1·44), $\lambda_{max.}$ 230 and 272 mμ (ε 16,600 and 9300 respectively) (Found: C, 78·75; H, 9·05. $C_{35}H_{46}O_4$ requires C, 78·9; H, 9·1%).

14-*Methyl*-7 : 11-*dioxocholestan*-3β-*yl Benzoate*.—14-Methyl-7 : 11-dioxocholest-8-en-3β-yl benzoate (220 mg.) in glacial acetic acid (15 ml.) was refluxed with zinc dust (250 mg.) for 1 hr.

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Crystallisation of the product from chloroform–methanol gave **14-*methyl*-7 : 11-*dioxocholestan*-3β-*yl benzoate***, m. p. 168°, $[\alpha]_D$ +52° (*c* 1·50) (Found : C, 78·35; H, 9·75. $C_{35}H_{50}O_4$ requires C, 78·6; H, 9·4%).

Conversion of **14-*Methyl*-7 : 11-*dioxocholestan*-3β-*yl Benzoate into* 14-*Methylcholestan*-3β-*ol and its Derivatives***.—The diketone (420 mg.) was reduced by the modified Wolff–Kishner method as applied for the preparation of lanostanol.[18] Rebenzoylation of the product and crystallisation from chloroform–methanol gave **14-*methylcholestan*-3β-*yl benzoate*** (280 mg.), m. p. 167—168°, $[\alpha]_D$ +32° (*c* 1·86), undepressed in m. p. on admixture with an authentic specimen of comparable physical constants prepared by benzoylation of the 14-methylcholestanol from lanostenol [19] (Found : C, 82·9; H, 10·8. $C_{35}H_{54}O_2$ requires C, 82·95; H, 10·75%). The identity was further checked by hydrolysis to 14-methylcholestanol {m. p., mixed m. p., and $[\alpha]_D$ +39° (*c* 1·28)} and by acetylation of the latter to 14-methylcholestanyl acetate (m. p. and mixed m. p.).

4 : 4 : 14-*Trimethyl*-15-*oxocholest*-7-*en*-3β-*yl Benzoate*.—To potassium (1·4 g.) in dry *tert.*-butyl alcohol (40 ml.) there was added 4 : 4-dimethyl-15-oxocholest-8(14)-en-3β-yl benzoate (see above) (326 mg.) in methyl iodide (5·25 ml.). The solution was stirred until neutral. The product, crystallised from chloroform–methanol, afforded **4 : 4 : 14-*trimethyl*-15-*oxocholest*-7-*en*-3β-*yl benzoate*** (225 mg.), m. p. 212—213°, $[\alpha]_D$ +84° (*c* 1·42), $\lambda_{max.}$ 229, 273, and 281 mμ (ε 15,200, 1000, and 800 respectively) (Found : C, 80·95; H, 9·8. $C_{37}H_{54}O_3$ requires C, 81·25; H, 9·95%).

The 15-oxo-benzoate (see above) (100 mg.) was added to diethylene glycol (10 ml.) containing dissolved sodium (200 mg.) at 175°. Anhydrous hydrazine, prepared by refluxing 95% hydrazine for 7 hr. under nitrogen with an equal weight of sodium hydroxide pellets, was distilled in until the mixture refluxed at 175°. The refluxing was continued for 12 hr., then excess of hydrazine was distilled off until the temperature reached 210°, which temperature was then held for 24 hr. All operations were carried out under nitrogen in an all-glass apparatus protected against moisture. Crystallisation of the product from ether–methanol gave lanost-7-enol (52 mg.), identified by m. p., rotation {$[\alpha]_D$ +10° (*c* 1·45)}, and analysis (Found : C, 83·9; H, 12·15. Calc. for $C_{30}H_{52}O$: C, 84·05; H, 12·25%). The identity was confirmed by conversion into the acetate {m. p., mixed m. p., $[\alpha]_D$ +27° (*c* 1·27), infrared spectrum, and analysis (Found : C, 81·65; H, 11·55. Calc. for $C_{32}H_{54}O_2$: C, 81·45; H, 11·7%)}.

Lanost*-7-*enyl Benzoate and its Equilibrium with Lanost*-8-*enyl Benzoate.—Lanost-7-enol (prepared *via* the acetate according to Marker, Wittle, and Mixon [20]) was converted into the *benzoate* with pyridine–benzoyl chloride. Recrystallised from chloroform–methanol, this had m. p. 207—208°, $[\alpha]_D$ +51° (*c* 1·09) (Found : C, 83·3; H, 10·5. $C_{37}H_{56}O_2$ requires C, 83·4; H, 10·4%).

Lanost-7-enyl benzoate (1·0 g.) in dry chloroform (50 ml.) was treated with hydrogen chloride gas at room temperature for 2 hr. The product was carefully chromatographed over alumina. The first fraction (228 mg.), eluted with 4 : 1 light petroleum (b. p. 40—60°)–benzene, had m. p. (from chloroform–methanol) 193—195°, $[\alpha]_D$ +71° (*c* 1·80), undepressed in m. p. on admixture with an authentic specimen of m. p. 194—195° and $[\alpha]_D$ +71°. The identity was confirmed by hydrolysis to lanostenol {m. p., mixed m. p., and $[\alpha]_D$ +59° (*c* 1·35)} and by acetylation of the latter to lanostenyl acetate {m. p., mixed m. p. and $[\alpha]_D$ +60° (*c* 1·76)}.

Oxidation of Lanostenyl Acetate to* 7 : 11-*Dioxotrisnorlanostenoloic Acid Acetate.—7 : 11-Dioxolanostenyl acetate, prepared by oxidation of lanostenyl acetate [26] (28 g.) in glacial acetic acid (700 ml.) and acetic anhydride (28 ml.), was treated with chromium trioxide (60 g.) in water (70 ml.), acetic acid (280 ml.), and concentrated sulphuric acid (14 ml.), added slowly at room temperature, and the solution was stirred overnight. Dilution with water and extraction with benzene (washed well with water) gave a product (14 g.) which, on chromatography over alumina and elution with 4 : 1 methanol–acetic acid, gave 7 : 11-dioxotrisnorlanostenoloic acid acetate (4·6 g.), identified by m. p. (192—194°, from chloroform–light petroleum), mixed m. p., and rotation {$[\alpha]_D$ +96° (*c* 1·27)}. The identity was confirmed by alkaline hydrolysis to 7 : 11-dioxotrisnorlanostenoloic acid, identified by m. p. (202—204° from aqueous methanol), mixed m. p., and rotation {$[\alpha]_D$ +103° (*c* 1·19)}. The authentic specimens of acetate and alcohol [27] had m. p. 193—194°, $[\alpha]_D$ +96° (*c* 1·37), and m. p. 202—204°, $[\alpha]_D$ +103° (*c* 1·78), respectively. The identity was further confirmed by conversion of the acetate into the acetate methyl ester, identified by m. p. (140—142° from methanol), mixed m. p., and rotation {$[\alpha]_D$ +94° (*c* 2·06)}. The authentic acetate methyl ester [27] had m. p. 140—142°, $[\alpha]_D$ +94° (*c* 1·32).

[26] Ruzicka, Rey, and Muhr, *Helv. Chim. Acta*, 1944, **27**, 472.
[27] Voser, Jeger, and Ruzicka, *ibid.*, 1952, **35**, 497.

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Methyl 11-*Oxotrisnorlanost*-8-*enoloate Acetate*.—Methyl 7 : 11-dioxotrisnorlanostenoloate acetate (see above) (5 g.) was heated with 60% hydrazine hydrate (5 ml.) in diethylene glycol (200 ml.) for 1 hr. at 200° under reflux. The solution was cooled and sodium (5 g.), dissolved in diethylene glycol (80 ml.), added; refluxing was continued for a further 6 hr. Methylation (diazomethane), acetylation (pyridine–acetic anhydride on the steam-bath for 1 hr.), and chromatography over alumina gave *methyl* 11-*oxotrisnorlanost*-8-*enoloate acetate* (2·1 g.), m. p. (from methanol) 145—149°, $[\alpha]_D$ +129° (*c* 1·64), $\lambda_{max.}$ 256 mμ (ε 7600) (Found : C, 74·1; H, 9·4. $C_{30}H_{46}O_5$ requires C, 74·05; H, 9·55%).

Methyl Trisnorlanost-8-*enoloate Acetate*.—(a) *From methyl* 11-*oxotrisnorlanost*-8-*enoloate acetate*. The ketone (see above) (2·1 g.) was added to a solution of sodium (1·0 g.) in diethylene glycol (50 ml.) at 180° and freshly prepared anhydrous hydrazine was distilled in until the solution refluxed freely. The refluxing was continued at 180° for 24 hr. and then the temperature was raised to 210° by distilling off hydrazine. The refluxing period at 210° was prolonged for a further 24 hr. The product, when methylated (diazomethane), acetylated (pyridine–acetic anhydride on the steam-bath for 1 hr.), and chromatographed, gave *methyl trisnorlanost*-8-*enoloate acetate* (700 mg.), m. p. (from chloroform–methanol) 174—176°, $[\alpha]_D$ +58° (*c* 1·65) (Found : C, 76·2; H, 10·35. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·25%). The application of the vigorous Wolff–Kishner reduction conditions to an 8-unsaturated 7 : 11-dioxo-compound directly, such as 7 : 11-dioxolanostenyl acetate, gave only the fully saturated compound (lanostanol) in approximately the same yield as starting with the saturated diketone (7 : 11-dioxolanostanyl acetate).

(b) *From " lanosteryl acetate."* " Lanosteryl acetate " (6·0 g.) (from acetylation of technical " lanosterol "), suspended in chloroform (250 ml.), was ozonised at −60° until the solution was clear. Zinc dust (1·0 g.) and acetic acid (20 ml.) were added and the solution was allowed to warm to room temperature with stirring. The crude product in " AnalaR " acetone (500 ml.) was treated with potassium permanganate (500 mg.) in water (20 ml.) and left at room temperature for 1½ hr. The excess of permanganate was destroyed with sulphur dioxide, and the solution diluted with water and extracted with benzene. The crude product was chromatographed over alumina. Elution with 4 : 1 methanol–acetic acid gave an acid fraction which on methylation (diazomethane) and filtration in benzene through alumina afforded methyl trisnorlanost-8-enoloate acetate (1·25 g.), m. p. 174—176°, $[\alpha]_D$ +58° (*c* 1·20), undepressed in m. p. on admixture with material prepared as under (*a*) above. The ozonolysis route is the more convenient procedure for the preparation of this compound.

Methyl Bisnorlanost-8-*enoloate Acetate*.—Methyl trisnorlanost-8-enoloate acetate (1·3 g.) was hydrolysed with 5% methanolic potassium hydroxide, and the resulting alcohol-acid reacetylated (pyridine–acetic anhydride on the steam-bath for 1 hr.). The acetate acid thus formed was left overnight in sodium-dried benzene (5 ml.) with oxalyl chloride [24] (1 ml.) at 0°. The benzene and excess of oxalyl chloride were removed *in vacuo* and the residual acid chloride in dry ether (100 ml.) was added slowly with good stirring to an excess of diazomethane in the same solvent. The solution was left at room temperature for 90 min. and the ether then removed *in vacuo* at the same temperature. The crude diazo-ketone in dry methanol (75 ml.) was treated with silver oxide (100 mg.) (see ref. 28) at 50° for 1 hr. and then refluxed for 15 min. The solvent was removed *in vacuo* and the product chromatographed over alumina in benzene, to give *methyl bisnorlanost*-8-*enoloate acetate* (750 mg.), m. p. (from chloroform–methanol) 133—134°, $[\alpha]_D$ +64° (*c* 1·75) (Found : C, 76·75; H, 10·25. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·35%).

3β-*Acetoxylanost*-8-*en*-25-*ol*.—Methyl iodide (7·5 g.) in dry ether (20 ml.) was added slowly to magnesium turnings (1·5 g.) under dry ether (80 ml.) and the mixture stirred and refluxed for 1 hr. Methyl bisnorlanost-8-enoloate acetate (see above) (1·0 g.) in dry ether (50 ml.) was added and the solution refluxed overnight. The crude product, after re-acetylation with pyridine–acetic anhydride on the steam-bath for 1 hr., was chromatographed over alumina. Elution with benzene gave 3β-*acetoxylanost*-8-*en*-25-*ol* (400 mg.), m. p. (from methanol) 167—169°, $[\alpha]_D$ +71° (*c*, 1·15) (Found : C, 78·95; H, 11·1. $C_{32}H_{54}O_3$ requires C, 78·95; H, 11·2%). The crystalline alcohol (220 mg.) in xylene (20 ml.) was refluxed for 4 hr. with activated fuller's earth (210 mg.). After filtration over alumina in 1 : 1 light petroleum (b. p. 40—60°)–benzene the product had m. p. (from chloroform–methanol) 145—155° and was clearly a mixture. It

[24] " Syntheses using Diazomethane," Newer Methods of Preparative Organic Chemistry, Interscience Publ., New York, 1948.

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was depressed in m. p. on admixture with either the starting material or lanosterol acetate and showed a strong methylene band at 885 cm.$^{-1}$.

Methyl 11-Oxobisnorlanost-8-enoloate Acetate and Related Products.—Methyl 11-oxotrisnorlanost-8-enoloate acetate (see above) was converted *via* the corresponding acetate acid by Arndt–Eistert homologation into *methyl 11-oxobisnorlanost-8-enoloate acetate*, as described above for the 11-deoxo-analogue. Recrystallised from methanol, the 11-oxo-ester had m. p. 150—153°, $[\alpha]_D$ +127° (*c* 1·22) (Found: C, 74·45; H, 9·6. $C_{31}H_{48}O_5$ requires C, 74·35; H, 9·65%). It was treated with methylmagnesium iodide and further processed as described above, except that it was advantageous to carry out the reacetylation at room temperature overnight. Crystallisation of the chromatographed product from aqueous methanol afforded 3β-*acetoxy*-11-*oxolanost*-8-*en*-25-*ol*, m. p. 192—195°, $[\alpha]_D$ +133° (*c* 1·48) (Found: C, 76·9; H, 10·55. $C_{32}H_{52}O_4$ requires C, 76·75; H, 10·45%). This alcohol (200 mg.) in dioxan (42·5 ml.) and concentrated sulphuric acid (2·5 ml.) was left at room temperature overnight. The product was reacetylated for 1 hr. on the steam-bath with pyridine (2 ml.) and acetic anhydride (1 ml.). Chromatography over alumina in benzene and crystallisation from chloroform–methanol gave 11-oxolanosta-8 : 24-dienyl acetate (see below), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +125° (*c* 1·03)}. The identity was checked by hydrolysis to the corresponding alcohol (m. p. and mixed m. p.).

7 : 11-*Dioxolanosta*-8 : 24-*dienyl Acetate*.—Lanosterol acetate dibromide (main isomer, prepared according to directions kindly supplied by Dr. J. F. McGhie [25]) (9·0 g.), suspended in acetic acid (450 ml.), was treated at room temperature with chromium trioxide (10·0 g.) in the minimum of water. Concentrated sulphuric acid (4·5 ml.) was added cautiously and the solution stirred overnight at the same temperature. The solution was diluted with water and extracted with ether, and the ethereal layer washed with water. After removal of the ether *in vacuo* the crude product was filtered through alumina in 1 : 1 benzene–ether to remove acidic impurities. The eluted material in acetone (200 ml.) was refluxed for 4 hr. with sodium iodide (25 g.) in the same solvent (200 ml.). Dilution with water, extraction with benzene, washing with sodium thiosulphate solution (to remove iodine), and removal of the benzene *in vacuo* gave a crude product which, on crystallisation from methanol, afforded 7 : 11-*dioxolanosta*-8 : 24-*dien*-3β-*yl acetate* (2·1 g.), m. p. 143—144°, $[\alpha]_D$ +81° (*c* 1·13), $\lambda_{max.}$ 272 mμ (ε 9100) (Found: C, 76·9; H, 9·65. $C_{32}H_{48}O_4$ requires C, 77·35; H, 9·75%).

11-*Oxolanosta*-8 : 24-*dien*-3β-*yl Acetate*.—7 : 11-Dioxolanosta-8 : 24-dien-3β-yl acetate (see above) (2·0 g.) in diethylene glycol (100 ml.) and 60% hydrazine hydrate (2·5 ml.) were refluxed for 1 hr. Sodium (2·5 g.) in diethylene glycol (40 ml.) was added and the solution refluxed for a further 6 hr. The crude product was reacetylated with pyridine–acetic anhydride on the steam-bath and chromatographed over alumina to furnish 11-*oxolanosta*-8 : 24-*dien*-3β-*yl acetate* (850 mg.), m. p. (from aqueous methanol) 112—113°, $[\alpha]_D$ +125° (*c* 1·06) (Found: C, 79·65; H, 10·3. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·45%). Alkaline hydrolysis in the usual way gave 11-*oxolanosta*-8 : 24-*dien*-3β-*ol*, m. p. (from aqueous methanol) 135—136°, $[\alpha]_D$ +98° (*c* 0·57) (Found: C, 81·85; H, 11·15. $C_{30}H_{48}O_2$ requires C, 81·75; H, 11·0%).

11-Oxolanosta-8 : 24-dien-3β-yl acetate (450 mg.) was added to a solution of sodium (1·0 g.) in diethylene glycol (50 ml.). The solution was heated to 180° and anhydrous hydrazine (see above) distilled in until the solution refluxed at this temperature. The refluxing was continued overnight, the temperature raised to 210° by distilling out some of the hydrazine, and refluxing continued at this temperature for 24 hr. The crude product was reacetylated with pyridine–acetic anhydride on the steam-bath and then chromatographed over alumina in benzene solution. Crystallisation from chloroform–methanol gave lanosteryl (lanosta-8 : 24-dienyl) acetate, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +58° (*c* 1·87)}.

Conversion of 11-*Oxolanosta*-8 : 24-*dien*-3β-*yl Acetate into Agnosteryl Acetate*.—The 11-oxo-acetate (1·0 g.) in sodium-dried ether (150 ml.) was refluxed with lithium aluminium hydride (750 mg.) for 4 hr. Crystallisation of the product from chloroform–methanol gave *lanosta*-8 : 24-*diene*-3β : 11β-*diol* (750 mg.), m. p. 153—155°, $[\alpha]_D$ +58° (*c* 1·19) (Found: C, 82·2; H, 11·6. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%). The diol (800 mg.) was refluxed in acetic anhydride (50 ml.) with toluene-*p*-sulphonic acid (10 mg.) for 1 hr. Filtration of the product in benzene through alumina afforded agnosteryl acetate [lanosta-7 : 9(11) : 24-trien-3β-yl acetate] (600 mg.), m. p. (from chloroform–methanol) 180—181°, $[\alpha]_D$ +90° (*c* 1·59), $\lambda_{max.}$ 236, 243, 252 mμ (ε 14,700, 17,400, and 11,400 respectively). The m. p., rotation, and absorption

intensity are all slightly higher [28] than the recorded constants.[29] However, the value of ε at $\lambda_{max.}$ 243 mμ corresponds almost exactly with that recorded for lanosta-7 : 9(11)-dien-3β-yl acetate.[30]

We are indebted to Messrs. Glaxo Laboratories Ltd. for a generous supply of pure 7-dehydrocholesterol. One of us (D. A. J. I.) thanks the International Wool Secretariat for a Pre-doctorate Fellowship. This work was carried out by another of us (A. A. P.) during the tenure of an Ethyl Corporation Pre-doctoral Fellowship. We also acknowledge the receipt of a Beaverbrook Scholarship (R. B. K.).

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[28] Ruzicka, Denss, and Jeger, *Helv. Chim. Acta*, 1946, **29**, 204.
[29] Barton, Fawcett, and Thomas, *J.*, 1951, 3147.

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225. *Action of Acidic Reagents on Methyl 2-Arylvinylcarbamates.*

By K. W. GOPINATH, T. R. GOVINDACHARI, K. NAGARAJAN, and K. K. PURUSHOTHAMAN.

N-2-Arylvinylcarbamates with activating substituents in the ring are converted into 2-arylnaphthalenes by acidic reagents. With phosphorus oxychloride, methyl styrylcarbamate yields predominantly 3 : 5-diphenylpyridine.

DEY and PARIKSHIT [1] obtained in high yield a neutral nitrogen-free compound, m. p. 200°, by the action of alcoholic hydrogen chloride or phosphorus oxychloride in toluene or hot dilute sulphuric acid on methyl *N*-3 : 4-methylenedioxystyrylcarbamate. In a re-investigation we found that the melting point and analysis agreed with those for 2 : 3-methylenedioxy-6-(3 : 4-methylenedioxyphenyl)naphthalene,[2] and that its ultraviolet absorption was that of a 2-arylnaphthalene. The compound should have resulted by the condensation of two molecules of homopiperonaldehyde produced by hydrolysis of the carbamate.

2 : 3-Dimethoxy-6-(3 : 4-dimethoxyphenyl)naphthalene was similarly prepared from methyl *N*-(3 : 4-dimethoxystyryl)carbamate and its melting point and absorption spectrum agreed with those reported by Bailey, Robinson, and Staunton [3] who had obtained it by dehydrogenation of a by-product in the Leuckart reaction on 2-(3 : 4-dimethoxyphenyl)-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-oxonaphthalene. The structure was confirmed by comparison with a specimen synthesised as follows: Veratrole was subjected to a Friedel–Crafts reaction with 3 : 4-dimethoxyphenylsuccinic anhydride, to give α-(3 : 4-dimethoxyphenyl)-β-veratroylpropionic acid. Clemmensen reduction followed by cyclisation then gave the tetralone, which by a second Clemmensen reduction followed by dehydrogenation yielded 6-(3 : 4-dimethoxyphenyl)-2 : 3-dimethoxynaphthalene.

2-Methoxy-6-*m*-methoxyphenyl-, 6-(2 : 3-dimethoxyphenyl)-1 : 2-dimethoxy-, and 6-(2 : 5-dimethoxyphenyl)-1 : 4-dimethoxy-naphthalene have also been prepared in fair yield from the corresponding carbamates. The action of phosphoric oxide on methyl 2-β-naphthyl- and 2-9′-phenanthryl-vinylcarbamate gave products in *ca.* 1·5 and 25% yield respectively to which, in analogy with the previous examples, the structures 2-β-naphthylphenanthrene and 6-9′-phenanthryltriphenylene may be assigned. Under the same conditions methyl 2-α-naphthylvinylcarbamate yielded a nitrogen-containing compound which was not further investigated.

Treatment of methyl styrylcarbamate with cold alcoholic hydrogen chloride or with

[1] Dey and Parikshit, *Proc. Nat. Inst. Sci. India*, 1945, **11**, 37.
[2] Erdtman and Robinson, *J.*, 1933, 1530.
[3] Bailey, Robinson, and Staunton, *J.*, 1950, 2277.

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phosphorus oxychloride in boiling toluene led to uncrystallisable resins. The last reagent in cold benzene, however, gave a neutral, unidentified compound, $C_{14}H_{15}O_2N$, and a base, $C_{17}H_{13}N$, m. p. 138—139°, in *ca.* 30—40% yield. The base yielded, readily in the cold, a methiodide which was oxidised by aqueous potassium permanganate to benzoic acid. The base could not be reduced in neutral or acid solution, but its methiodide was reduced in methanol in presence of Adams catalyst, with absorption of 3 mols. of hydrogen, to a mixture of two isomeric bases separated by crystallisation of the hydrochlorides. The major product was converted by a two-stage Hofmann degradation into a nitrogen-free oil which yielded only benzoic acid on oxidation. This observation taken in conjunction with the molecular formula suggested that the base could be a diphenylpyridine, and its properties corresponded with those of 3 : 5-diphenylpyridine prepared recently by Eliel, McBride, and Kaufmann;[4] comparison with a sample kindly provided by Dr. E. L. Eliel confirmed the identity. Incidentally, it may be noted that two products are formed by reduction of 3 : 5-diphenylpyridine methiodide, the major product being presumably the more stable *cis*-1-methyl-3 : 5-diphenylpiperidine.

Experimental

Ultraviolet measurements are for 95% ethanol solutions.

2 : 3-*Methylenedioxy*-6-(3 : 4-*methylenedioxyphenyl*)*naphthalene*.—A solution of methyl *N*-(3 : 4-methylenedioxystyryl)carbamate[1] (2 g.) in alcohol (50 ml.) was saturated at 0° with hydrogen chloride. The precipitate, recrystallised from acetic acid, gave the naphthalene (1·1 g.), m. p. 200—201°, $\lambda_{max.}$ 233, 260, 305 mμ (log ε 4·60, 4·52, 4·24) (Found: C, 74·0; H, 3·8. Calc. for $C_{18}H_{12}O_4$: C, 74·0; H, 4·1%) (Erdtman and Robinson[2] reported m. p. 201°). The naphthalene could also be got from the carbamate by the action of phosphorus oxychloride or phosphoric oxide in boiling toluene.

6-(3 : 4-*Dimethoxyphenyl*)-2 : 3-*dimethoxynaphthalene*.—3 : 4-*Dimethoxycinnamamide*. 3 : 4-Dimethoxycinnamic acid[5] (10 g.) in benzene (50 ml.) was refluxed with thionyl chloride (10 ml.) at 100° for 1 hr. The resulting solution was added gradually to an excess of aqueous ammonia (*d* 0·9) at 0° with stirring during 2 hr. The precipitate was filtered off and washed with water. Crystallisation from alcohol gave the amide (8 g.), m. p. 166° (Found: C, 64·0; H, 6·6; N, 6·8. Calc. for $C_{11}H_{13}O_3N$: C, 63·8; H, 6·3; N, 6·8%) (Lorz *et al.*[6] reported m. p. 166·5°).

Methyl N-3 : 4-*dimethoxystyrylcarbamate*. The foregoing amide (8 g.) dissolved in the minimum quantity of cold methanol was treated slowly with 5% aqueous sodium hypochlorite[7] (48·8 ml.) with good shaking. The mixture was heated at 100° for a few minutes and cooled. The precipitate was crystallised from alcohol, to give the *carbamate* (5·4 g.), m. p. 104° (Found: C, 60·7; H, 6·3; N, 6·0. $C_{12}H_{15}O_4N$ requires C, 60·8; H, 6·3; N, 5·9%).

6-(3 : 4-*Dimethoxyphenyl*)-2 : 3-*dimethoxynaphthalene*. The above carbamate (2 g.) in alcohol (30 ml.) was saturated with hydrogen chloride at 0°, evaporated to the point of crystallisation, and left at 0°. The precipitate, on recrystallisation from alcohol, gave the *naphthalene* (1 g.), m. p. 178°, undepressed on admixture with another specimen (see below), $\lambda_{max.}$ 230, 260, 295 mμ (log ε 4·47, 4·53, 4·36) (Found: C, 74·2; H, 6·3. $C_{20}H_{20}O_4$ requires C, 74·1; H, 6·2%).

6-(2 : 3-*Dimethoxyphenyl*)-1 : 2-*dimethoxynaphthalene*.—2 : 3-Dimethoxycinnamic acid[8] (8 g.) was converted through the *amide* (6 g.), m. p. 131° (Found: C, 64·2; H 6·2; N, 6·7%), into *methyl* N-2 : 3-*dimethoxystyrylcarbamate* (3·8 g.), m. p. 138° (from dilute alcohol) (Found: C, 61·0; H, 6·0; N, 5·7%). Treatment of this with alcoholic hydrogen chloride did not give the naphthalene. The carbamate (2 g.), dry toluene (16 ml.), and phosphorus oxychloride (6 ml.) were refluxed for 3 hr. The mixture was decomposed with ice, and the neutral material from the product chromatographed in benzene over alumina. The residue from the eluate crystallised from dilute alcohol or light petroleum, to yield needles of 6-(2 : 3-*dimethoxyphenyl*)-1 : 2-*dimethoxynaphthalene* (0·25 g.), m. p. 68—69°, $\lambda_{max.}$ 230, 253, 290 mμ (log ε 4·67, 4·70, 4·05) (Found: C, 74·2; H, 6·3%).

[4] Eliel, McBride, and Kaufmann, *J. Amer. Chem. Soc.*, 1953, **75**, 4291.
[5] Robinson and Shinoda, *J.*, 1925, **127**, 1977.
[6] Lorz, Albro, and Baltzly, *J. Amer. Chem. Soc.*, 1951, **73**, 483.
[7] Weerman, *Annalen*, 1913, **401**, 6.
[8] Haworth, *J.*, 1927, 2282.

6-(2 : 5-*Dimethoxyphenyl*)-1 : 4-*dimethoxynaphthalene*.—2 : 5-Dimethoxycinnamic acid[9] (8 g.) gave the *amide* (7·2 g.), m. p. 168° (from alcohol) (Found : C, 64·2; H, 6·2; N, 6·7%), and then *methyl* N-(2 : 5-*dimethoxystyryl*)*carbamate* (5 g.), m. p. 97° (from dilute alcohol) (Found : C, 61·0; H, 6·3; N, 6·1%). An alcoholic solution of the carbamate (1 g.) was saturated with hydrogen chloride and then evaporated. The residue was washed with water and dried. Purification by chromatography gave 6-(2 : 5-*dimethoxyphenyl*)-1 : 4-*dimethoxynaphthalene* (0·3 g.) as light greenish-yellow cubes (from alcohol), m. p. 99°, $\lambda_{max.}$ 220, 255, 310 mμ (log ε 4·65, 4·45, 4·10) (Found : C, 74·2; H, 6·1%).

2-*Methoxy*-6-m-*methoxyphenylnaphthalene*.—3-Methoxycinnamic acid[10] (6 g.) gave the *amide* (4·7 g.), m. p. 133° (from alcohol) (Found : C, 67·6; H, 6·6; N, 8·0. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·2; N, 7·9%), which in turn yielded *methyl* N-3-*methoxystyrylcarbamate* (2·7 g.), m. p. 111° (from alcohol) (Found : C, 64·2; H, 5·9; N, 7·0. $C_{11}H_{13}O_2N$ requires C, 63·8; H, 6·3; N, 6·8%). Treatment of this with alcoholic hydrogen chloride and purification of the product by chromatography gave 2-*methoxy*-6-m-*methoxyphenylnaphthalene* (0·4 g.), m. p. 92° (from alcohol), $\lambda_{max.}$ 225, 255, 297 mμ (log ε 4·55, 4·60, 4·20) (Found : C, 81·4; H, 6·5. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%).

Action of Phosphorus Oxychloride on Methyl 2-α-*Naphthylvinylcarbamate*.—β-1-Naphthylacrylic acid[11] (10 g.) gave the amide (9 g.), m. p. 173° (Found : C, 79·3; H, 5·6; N, 7·0. Calc. for $C_{13}H_{11}ON$: C, 79·2; H, 5·6; N, 7·1%) (Jensen and Christenson[11] recorded m. p. 172—173°), which yielded methyl 2-α-naphthylvinylcarbamate (4·2 g.), m. p. 121° (from alcohol) (Found : C, 74·2; H, 5·6; N, 6·4. Calc. for $C_{14}H_{13}O_2N$: C, 74·0; H, 5·7; N, 6·2%) (Jensen and Christenson[11] recorded m. p. 121°). Treatment of the carbamate with alcoholic hydrogen chloride failed to yield crystallisable material. The carbamate (1 g.) was refluxed with phosphorus oxychloride (3 ml.) in toluene (10 ml.) for 3 hr. Purification of the neutral matter from the reaction by chromatography and crystallisation from alcohol gave an unidentified *compound* as greenish-yellow needles (0·2 g.), m. p. 168° (Found : C, 84·5; H, 5·8; N, 4·2. $C_{21}H_{17}ON$ requires C, 84·3; H, 5·7; N, 4·7%). This was obtained also by the use of phosphoric oxide instead of oxychloride.

2-2′-*Naphthylphenanthrene*.—β-2-Naphthylacrylic acid[12] (10 g.) was converted through the *amide* (8·5 g.), m. p. 193° (from alcohol) (Found : C, 79·6; H, 5·6; N, 7·2%), into *methyl* 2-2′-*naphthylvinylcarbamate* (3·7 g.), m. p. 122° (from benzene) (Found : C, 73·3; H, 6·1; N, 6·2%). This (1 g.) was refluxed with phosphoric oxide (5 g.) in xylene (10 ml.) for 2 hr. The neutral matter from the product was passed in benzene through alumina. The residue from evaporation of the eluate, after two crystallisations from alcohol, gave the *phenanthrene* (10 mg.), m. p. 234—235° (Found : C, 95·4; H, 4·9. $C_{24}H_{16}$ requires C, 94·7; H, 5·3%).

6-9′-*Phenanthryltriphenylene*.—2-9′-Phenanthrylacrylic acid[13] (5 g.) gave the *amide* (3·4 g.), m. p. 227° (from alcohol) (Found : C, 82·6; H, 5·0; N, 5·6. $C_{17}H_{13}ON$ requires C, 82·6; H, 5·3; N, 5·7%), and then *methyl* 2-9′-*phenanthrylvinylcarbamate* (1·5 g.), m. p. 155—157° (from benzene) (Found : C, 78·6; H, 5·0; N, 5·3. $C_{18}H_{15}O_2N$ requires C, 78·0; H, 5·4; N, 5·1%). The carbamate (0·5 g.) on being refluxed with phosphoric oxide (5 g.) in toluene (10 ml.) for 2 hr. and chromatographed (neutral product), gave the *hydrocarbon*, pale yellow cubes (from light petroleum, b. p. 60—80°), m. p. 214—216°, $\lambda_{max.}$ 260 mμ (log ε 5·10), $\lambda_{infl.}$ 303 mμ (log ε 4·45) (Found : C, 94·6; H, 5·3. $C_{32}H_{30}$ requires C, 95·0; H, 5·0%).

6-(3 : 4-*Dimethoxyphenyl*)-2 : 3-*dimethoxynaphthalene*.—α-(3 : 4-*Dimethoxyphenyl*)-β-*veratroylpropionic acid*. Veratrole (11 g.) and aluminium chloride (12 g.) were added to 3 : 4-dimethoxyphenylsuccinic anhydride (9·4 g.) in nitrobenzene (30 ml.) with stirring. After 48 hr. the mixture was decomposed with ice and hydrochloric acid and diluted with water (600 ml.). After removal of nitrobenzene by steam-distillation, the acid separated and was filtered off. More was obtained after precipitation of aluminium from the mother-liquor by sodium carbonate and acidification of the filtrate. The total acid (7·4 g.), after three crystallisations from alcohol, melted at 186—188° (Found : C, 64·5; H, 5·6. Calc. for $C_{20}H_{22}O_7$: C, 64·1; H, 6·0%) (Richardson, Robinson, and Seijo[14] reported m. p. 193—194°).

[9] Posternak and Castro, *Helv. Chim. Acta*, 1948, **31**, 536.
[10] Chakravarti, Haworth, and Perkin, *J.*, 1927, 2269.
[11] Jensen and Christenson, *Acta Chem. Scand.*, 1950, **4**, 703.
[12] Monier-Williams, *J.*, 1906, **89**, 277.
[13] Bachmann and Kloetzel, *J. Amer. Chem. Soc.*, 1937, **59**, 2207.
[14] Richardson, Robinson, and Seijo, *J.*, 1937, 835.

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(3 : 4-*Dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*oxonaphthalene*.—The preceding acid (5 g.) reduced by the Clemmensen procedure gave αγ-di-(3 : 4-dimethoxyphenyl)-butyric acid (3 g.) as a viscous oil. This was shaken with 50% sulphuric acid (35 ml.) at 100° for 15 min. and the mixture extracted with ether. The ethereal layer was washed with alkali and evaporated. Crystallisation of the residue from alcohol gave the tetralone (1 g.), m. p. 150° (Found : C, 70·1; H, 6·0. Calc. for $C_{20}H_{22}O_5$: C, 70·2; H, 6·4%) (Richardson *et al.*[14] give m. p. 147—149°).

6-(3 : 4-*Dimethoxyphenyl*)-5 : 6 : 7 : 8-*tetrahydro*-2 : 3-*dimethoxynaphthalene*.—The above tetralone (1 g.), reduced by the Clemmensen procedure, gave the *tetrahydronaphthalene*, m. p. 117° (from dilute alcohol) (Found : C, 73·5; H, 7·5. $C_{20}H_{24}O_4$ requires C, 73·2; H, 7·3%).

6-(3 : 4-*Dimethoxyphenyl*)-2 : 3-*dimethoxynaphthalene*.—The foregoing tetrahydronaphthalene (0·3 g.), dehydrogenated with 5% palladium–charcoal (0·2 g.) in *p*-cymene (40 ml.), gave the naphthalene, crystallising from alcohol as plates, m. p. 178° (Found : C, 74·3; H, 6·3%) (Bailey, Robinson, and Staunton [3] recorded m. p. 179—180°).

3 : 5-*Diphenylpyridine*.—A solution of methyl styrylcarbamate [7] (20 g.) in benzene (200 ml.) containing phosphorus oxychloride (60 ml.) was left at 30° for 5 days. After decomposition with ice, the aqueous acidic layer was separated, and the benzene layer extracted with N-hydrochloric acid (3 × 50 ml.). The combined acid extracts were shaken twice with ether, basified by addition of solid potassium carbonate, and extracted repeatedly with ether. Evaporation of the dried (KOH) extracts and crystallisation of the residue from alcohol gave 3 : 5-diphenylpyridine (3—4 g.) as plates, m. p. and mixed m. p. 137—138°, $\lambda_{max.}$ 245 (log ε 4·40), $\lambda_{infl.}$ 295 mμ (log ε 3·65) (Found : C, 88·3, 88·2; H, 5·5, 5·5; N, 6·1, 6·1. Calc. for $C_{17}H_{13}N$: C, 88·3; H, 5·6; N, 6·1%), yielding a picrate, yellow needles (from acetic acid), m. p. 201—202°, and a hydrochloride, needles (from alcohol–ether), m. p. 187—189°. The methiodide, prepared by methyl iodide in chloroform at 30°, formed pale yellow needles (from alcohol), m. p. 203—205°, $\lambda_{max.}$ 260, 315 mμ (log ε 4·40, 3·75) (Found : C, 57·6; H, 4·2; N, 4·0. Calc. for $C_{18}H_{16}NI$: C, 57·9; H, 4·3; N, 3·7%) (Eliel, McBride, and Kaufmann [4] reported m. p.s : picrate, 204—205·5°; hydrochloride, 194—195°; methiodide, 202—203°).

The acid-washed benzene solution from the reaction left on evaporation a gum which solidified on long contact with alcohol. Crystallisation from alcohol gave colourless needles of a neutral *substance* (Found : C, 73·3; H, 6·2; N, 6·4. $C_{14}H_{15}O_2N$ requires C, 73·4; H, 6·6; N, 6·1%).

Oxidation of 3 : 5-*Diphenylpyridine Methiodide*.—A suspension of the above methiodide (1 g.) in water (75 ml.) containing potassium permanganate (1 g.) was refluxed with addition of more of a 2·5% solution of the oxidant, till a pink colour persisted. The mixture was filtered and the manganese dioxide residue washed with hot water. The filtrate was concentrated to a small volume and saturated with sulphur dioxide. The precipitated benzoic acid, after crystallisation from water, had m. p. and mixed m. p. 120—121°.

cis- *and* trans-1-*Methyl*-3 : 5-*diphenylpiperidine*.—3 : 5-Diphenylpyridine methiodide (3·5 g.) in methanol (100 ml.) was shaken with hydrogen (60 lb./sq. in.) in the presence of Adams catalyst (0·35 g.) till absorption of hydrogen ceased (5 hr.; 3 mols.). The solution was filtered from the catalyst which was washed with more methanol. The filtrate was evaporated and the residual gum triturated with alkali. Extraction with ether and evaporation gave an oil (2·1 g.) which was treated in ether with hydrogen chloride. Addition of dry ether to an alcoholic solution of the precipitate gave needles of cis-1-*methyl*-3 : 5-*diphenylpiperidine hydrochloride* (0·7 g.), m. p. 209—212°, raised by a second crystallisation from the same solvent mixture to 215—217° (Found : C, 74·6, 74·6; H, 7·5, 7·6. $C_{18}H_{22}NCl$ requires C, 75·1; H, 7·7%) and yielding, by basification and ether-extraction, the base, needles (from light petroleum), m. p. 58—61°. The *methiodide*, obtained by methyl iodide in chloroform at 100°, formed plates (from alcohol), m. p. 233—234°, $\lambda_{infl.}$ 257 mμ (log ε 2·35) (Found : C, 57·8; H, 5·9. $C_{19}H_{24}NI$ requires C, 58·0; H, 6·1%).

The alcohol–ether mother-liquor from the crystallisation of the above hydrochloride was evaporated and the residue converted into the free base (0·65 g.) and then into the methiodide by methyl iodide in chloroform at 100°. The gum thus obtained was dissolved in alcohol and treated with small volumes of ether, step-wise. After the separation of more (0·3 g.) of the *cis*-methiodide, m. p. and mixed m. p. 232—234°, trans-1 : 1-*dimethyl*-3 : 5-*diphenylpiperidinium iodide* (0·15 g.) was obtained. Recrystallised from alcohol–ether, it had m. p. 231—234°, and mixed m. p. with the *cis*-isomer, 195—200°, $\lambda_{infl.}$ 257 mμ (log ε 2·66) (Found : C, 58·3, 58·4; H, 6·0, 6·3%).

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Degradation. The *cis*-methiodide (1 g.), 50% potassium hydroxide solution (20 ml.), and alcohol (20 ml.) were refluxed for 3 hr. The solution was cooled, diluted with water, and extracted with ether. The ether layer was dried (K_2CO_3) and treated with hydrogen chloride. Recrystallisation of the precipitate from alcohol–ether mixture gave the *methine hydrochloride* (0·6 g.), m. p. 205—206° (Found : C, 75·0; H, 8·0. $C_{19}H_{24}NCl$ requires C, 75·6; H, 7·6%). The *base*, got from the hydrochloride by basification and ether extraction, was an oil, b. p. 141—142°/0·05 mm. (Found : C, 85·9; H, 8·4. $C_{19}H_{23}N$ requires C, 86·0; H, 8·7%).

This base (1·2 g.), after being heated with methyl iodide (3 g.) in chloroform (20 ml.) for 2 hr., gave on evaporation a gummy methiodide. This was converted into the methohydroxide by shaking its aqueous solution for 3 hr. with silver oxide (from 5 g. of silver nitrate), filtering, and evaporating the filtrate to dryness at 50° *in vacuo*. The methohydroxide was boiled with 50% potassium hydroxide solution (20 ml.), and the product distilled with steam. The distillate was made acidic and extracted with ether. The ether layer was separated, washed with alkali and then with water and dried (Na_2SO_4). Evaporation left a pale yellow oil (0·4 g.), b. p. 88°/0·05 mm. (Found : C, 89·4; H, 7·3%).

This oil (0·4 g.) was treated with potassium permanganate (2·5 g.) in acetone (85 ml.). The solution was filtered. The manganese dioxide residue was boiled with water and filtered. The filtrate was concentrated and acidified. The precipitated benzoic acid, after crystallisation from water, had m. p. and mixed m. p. 120—121°.

We thank Dr. E. L. Eliel for gift of a specimen of 3 : 5-diphenylpyridine, the Government of India for a studentship (to K. W. G.), and Mr. S. Selvavinayagam for analyses.

PRESIDENCY COLLEGE, MADRAS, INDIA. [*Received, September 25th,* 1956.]

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226. *Chemistry of the Vitamin B_{12} Group. Part IV.*[1] *The Isolation of Crystalline Nucleotide-free Degradation Products.*

By R. BONNETT, J. R. CANNON, A. W. JOHNSON, and SIR ALEXANDER TODD.

The mixture of tetra-, penta-, and hexa-carboxylic acids formed on vigorous alkaline hydrolysis of vitamin B_{12} has been fractionated on an ion-exchange column. The pure pentacarboxylic acid so obtained has been crystallised in the form of its dicyanide, and the hexacarboxylic acid both as the dicyanide and as the monochloride monocyanide, the latter proving particularly suitable for *X*-ray studies. The combination of *X*-ray and chemical evidence has enabled structural formulæ to be advanced both for the hexacarboxylic acid (IV) and for vitamin B_{12} itself (VII). Separation of the mixture of tetra-, penta-, hexa-, and hepta-carboxylic acids obtained on vigorous acid hydrolysis of the vitamin has also been effected, but the individual acids have not yet been obtained crystalline.

IN Part III [1] of this series (where earlier work is cited) the behaviour of vitamin B_{12} under varying conditions of hydrolysis was reported and its polyamide character was recognised. These and earlier findings by us and others being taken into consideration the partial formula (I) was advanced for the vitamin. Hydrolysis of the vitamin gave a complex mixture of red cobalt-containing acids and by paper electrophoresis of hydrolysates it was found that according to the conditions of hydrolysis two series of acids could be recognised. The first series (mono- to hepta-carboxylic acids) lacked the benziminazole nucleotide while the second (mono- to hexa-carboxylic acids) still retained it in combination. The close similarity between the visible spectra of all these acids and of vitamin B_{12} itself suggested that the chromophore had been little altered by hydrolysis and hence that these acids would be of direct value in endeavouring to elucidate the structure of the cobalt-containing core of the vitamin. For structural study it seemed most desirable to obtain at least one of the nucleotide-free acids in a pure crystalline condition. It is the

[1] Part III, Armitage, Cannon, Johnson, Parker, Smith, Stafford, and Todd, *J.*, 1953, 3849.

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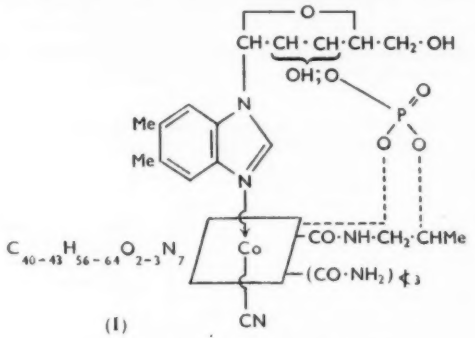
purpose of the paper to describe in detail how this object was attained, and to discuss the main structural features of one of the acids.

Although no conditions of hydrolysis have so far been discovered which yield a single product, treatment of vitamin B_{12} with 30% aqueous sodium hydroxide for one hour at 150° was found to yield a mixture containing mainly the nucleotide-free penta- and hexa-carboxylic acids with only a small amount of tetracarboxylic acid, and this method of



(I)

hydrolysis was adopted as the basis for isolation work. Electrophoresis on paper strips was clearly impracticable for preparative separation of the mixture of acids; it was indeed possible, by using Whatman " seed-testing " paper, to handle up to 50 mg. of material at one time but this represented the practical limit. Countercurrent distribution experiments were discouraging, and ion-exchange chromatography was therefore studied with Dowex 1 × 2 resin in which the degree of cross-linkage is small (*ca.* 2%) so that the cobalt-containing polycarboxylic acids can be readily eluted. The first success came from experiments in which the resin was used in the acetate form and dilute aqueous ammonium acetate was the eluting agent.

The alkaline hydrolysate was subjected in portions to preliminary electrophoresis on Whatman " seed-testing " paper, and the nucleotide separated from the tetra-, penta, and hexa-carboxylic acids; the crude hexacarboxylic acid fraction was then fractionated further on the ion-exchange column. Several minor fractions were eluted first, followed by the major band which was collected separately. After removal of inorganic salts an aqueous solution of the product was evaporated and the gummy residue dissolved in aqueous acetone, diluted with ether, and set aside. A small quantity of red prisms slowly separated; this sample of the hexacarboxylic acid was submitted to Dr. D. C. Hodgkin and the results of her elegant *X*-ray crystallographic studies on it have already been outlined.[2,3] Further dilution of the mother-liquor with ether yielded fine red needles; these were unsuitable for *X*-ray studies but were evidently a polymorphic form of the same hexacarboxylic acid since, on one occasion, the needle form was converted when kept in contact with the aqueous-acetone–ether mother-liquor into the prism form (identified by *X*-ray powder photography). Recrystallisation of the hexacarboxylic acid was best effected by cautious addition of ether to its aqueous-acetone solution although the process was rather wasteful. Analysis of a sample of the acid dried at 50° gave values which, if the degree of hydration is assumed to be that observed in the *X*-ray examination, correspond to a formula $C_{46}H_{60}O_{13}N_6CoCl,2H_2O$. This formula differs slightly from that mentioned in a preliminary communication [4] but it is clear that with molecules of this size precise definition of molecular formula by elementary analysis alone is hardly possible since a number of formulæ lie within the tolerance of the carbon and hydrogen values; the

[2] Brink, Hodgkin, Lindsey, Pickworth, Robertson, and White, *Nature*, 1954, **174**, 1169.
[3] Hodgkin, Pickworth, Robertson, Trueblood, Prosen, and White, *ibid.*, 1955, **176**, 325.
[4] Cannon, Johnson, and Todd, *ibid.*, 1954, **174**, 1168.

combined analytical and *X*-ray determinations, however, justify the formula quoted here. The infrared spectrum of the crystalline acid showed a band at 2141 cm.$^{-1}$ characteristic of the cyanide group and a solution of the acid in dilute nitric acid contained chloride ion. The absence of strong " aromatic bands " in the 690—870 cm.$^{-1}$ region of the infrared spectrum was also noteworthy. The ultraviolet and visible spectra of the acid (Figs. 1 and 2) both in water and in 0·1M-potassium cyanide strongly resemble those of vitamin B_{12}, showing the absence of any marked change in chromophore; differences in the

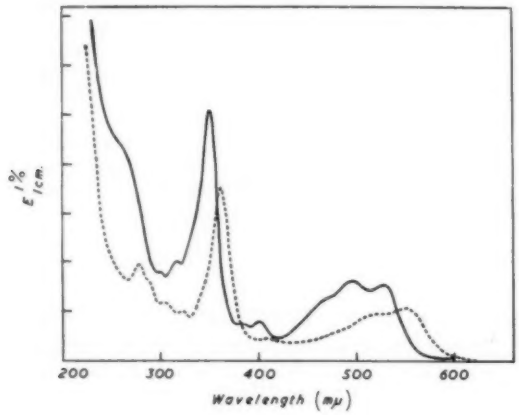


FIG. 1. *Ultraviolet absorption spectra of vitamin B_{12} (air-dried, – – – –) and the hexacarboxylic acid degradation product (——) in water.*

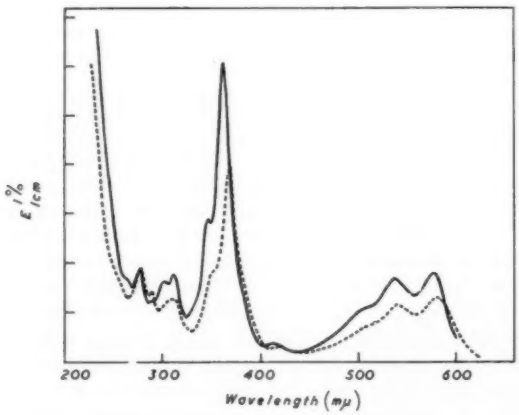


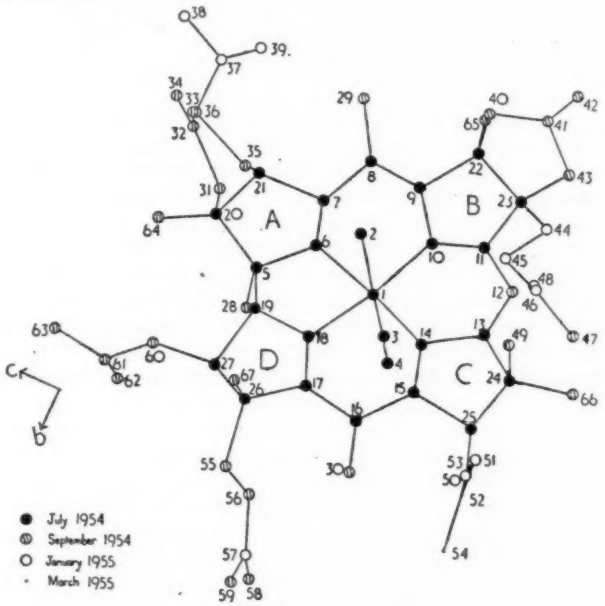
FIG. 2. *Ultraviolet absorption spectra of vitamin B_{12} (air-dried, – – – –) and the hexacarboxylic acid degradation product (——) in 0·1M-potassium cyanide.*

280 mμ region are attributable to the absence of the benziminazole nucleus in the hexacarboxylic acid.

Later studies suggested that the multiplicity of bands obtained by eluting electrophoretically homogeneous acids from ion-exchange columns with solutions of salts in the absence of excess of cyanide, as well as the reluctance of the acids to crystallise, is due, in part at least, to the ease of exchange of anions other than cyanide attached to the central cobalt atom. To overcome this difficulty and to establish a better standardised procedure for isolating hydrolysis products the above method leading to a chloro-cyanide was abandoned. Instead the ion-exchange resin was used in the chloride form and the chromatography carried out in presence of excess of cyanide. The mixed alkaline hydrolysate

was added to the column without preliminary electrophoresis, and the nucleotide was eluted with dilute acetic acid. The penta- and hexa-carboxylic acids in the dicyanide form were then successively eluted with dilute aqueous sodium chloride, again in the presence of cyanide. Aqueous-acetone solutions of the products, when kept at 0° in presence of hydrogen cyanide, yielded the dicyanides of the pentacarboxylic and hexacarboxylic acid in crystalline form. The hexacarboxylic acid derivative gave analytical values corresponding to $C_{47}H_{60}O_{13}N_7Co$ in agreement with the formula above deduced for the same acid in the monochloride-monocyanide form, while the pentacarboxylic acid dicyanide analysed as expected for $C_{47}H_{59-61}O_{12}N_8Co$. The ultraviolet and visible absorption spectra of both products again closely resembled those of vitamin B_{12}.

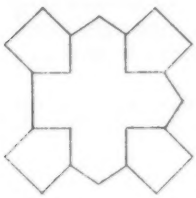
FIG. 3. *Atomic positions found in the hexacarboxylic acid derived from vitamin B_{12} projected on the* a *plane. The shading illustrates the course of the crystallographic study; the dates show approximately when each group of atoms was selected.*



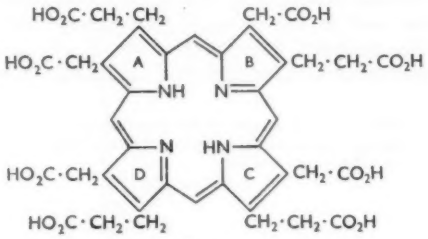
It has already been reported [1] that vigorous acid hydrolysis of vitamin B_{12} removes the nucleotide and aminopropanol residues, as well as amide groups, and yields mixtures of acids containing 4, 5, 6, and 7 carboxyl groups. These acids have now been separated by ion-exchange chromatography on Dowex 1 × 2 resin (chloride form), but none of them has so far been crystallised. Our knowledge of these acids is less than of the alkaline hydrolysis products, but it is clear that they are not identical with the latter and probably represent a separate series. No heptacarboxylic acid has ever been obtained except by acid hydrolysis; the hexacarboxylic acid obtained by alkaline hydrolysis is quite stable to further treatment with alkali.

In the initial phase of Dr. D. C. Hodgkin's *X*-ray analysis of the crystalline hexacarboxylic acid (as monochloride-monocyanide) obtained from alkaline hydrolysates as described above, the same central nucleus (II) containing four five-membered rings as occurs in vitamin B_{12} was recognised.[2] Further extension of the analysis determined the relative position of every atom (other than hydrogen) in the hexacarboxylic acid [3] and a projection of these positions is shown in Fig. 3. Much of the structure of the

hexacarboxylic acid follows at once from a consideration of Fig. 3 and the known chemical properties of the acid. It was known that the chlorine atom and the cyanide group were attached to the centrally situated cobalt atom, and analysis showed that the acid contained five nitrogen atoms in its molecule in addition to the one present in the cyanide group. The stability of the chromophoric system made it virtually certain that the other four atoms attached to the cobalt were nitrogen. The six carboxyl groups are clearly



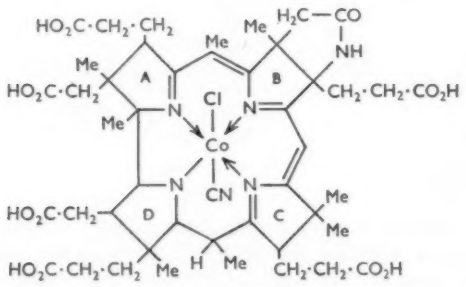
(II)



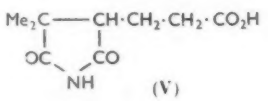
(III)

recognisable in Fig. 3 as occurring in four propionic acid and two acetic acid residues; all six residues form β-substituents on the five-membered rings, their arrangement being analogous to that known to occur in the natural porphyrin derivative (III) (uroporphyrin-III). Another projection of the electron-density pattern [3] shows that most of the inner portion of the molecule is flat but that the β-positions in the five-membered rings are all saturated; alternate β- and β′-positions are above and below the plane of the inner portion. All the propionic acid residues are situated on the same side of the molecule as the cyanide group, and the acetic acid residues and the chlorine atom project on the opposite side.

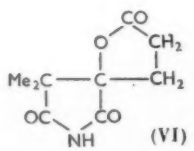
Ring B in the hexacarboxylic acid bears a β-methyl and a β′-propionic acid group as well as a ββ′-fused five-membered ring; the *X*-ray data suggest that this ring is either a lactone or a lactam and it is noteworthy that it does not occur in vitamin B_{12} itself which



(IV)



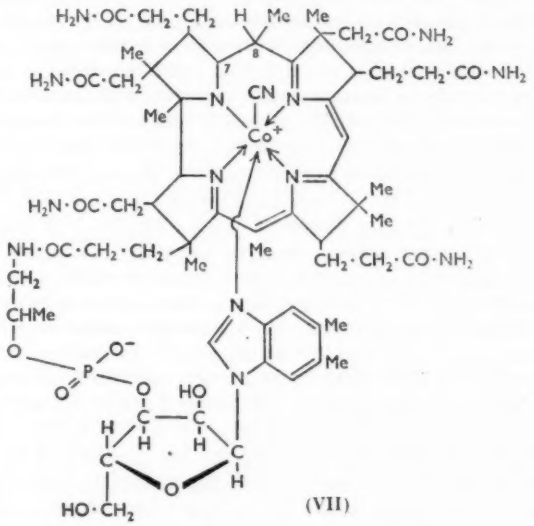
(V)



(VI)

appears to have methyl and acetamide groups as β-substituents and a propionamide group as a β′-substituent on ring B. The extra ring in the hexacarboxylic acid is therefore formed by a cyclisation involving either an acetamide or an acetic acid side-chain. The acid does not acquire an additional negative charge even at pH 11. This behaviour would be most remarkable for a lactone and, it being borne in mind that one of the nitrogen atoms in the acid is otherwise unaccounted for, the lactam formulation was adopted. Further support for this view comes from the presence of a band in the 1720 $cm.^{-1}$ region in the infrared spectrum of the hexacarboxylic acid. This frequency agrees with values quoted for the stretching frequency associated with the carbonyl group of a γ-lactam, but is very low for a γ-lactonic carbonyl group, which usually absorbs about 1770 $cm.^{-1}$. Further chemical

evidence for the γ-lactam structure derived from oxidation studies will be reported in a later communication. It should be noted that all the oxygen and nitrogen atoms required by the analytical values obtained for the hexacarboxylic acid monochloride-monocyanide (water of crystallisation being ignored) and the anhydrous dicyanide are accounted for by the foregoing considerations. In addition to the acetic and propionic acid side-chains there are eight single-atom (excluding hydrogen) substituents. It is reasonable to conclude



(VII)

that these are all methyl groups as the vitamin is re-formed on oxidation of its *leuco*-compound (apart from the displacement of the cyanide by a hydroxyl group [5]) and therefore contains no unsaturated side-chains. All these features were included in structure (IV) which was advanced for the hexacarboxylic acid in our preliminary communication.[6] Independent support for the structure of ring C in (IV) had also been provided by the isolation of the succinimides (V) and (VI) from the chromic acid oxidation products of a vitamin B_{12} acid hydrolysate,[7] and later the amide corresponding to (V) was isolated after a similar oxidation of the vitamin itself; [8] the imides (V) and (VI) are also found among the oxidation products of the pure hexacarboxylic acid.

The elucidation of the structure (IV) of the hexacarboxylic acid (we leave aside for the moment the question of number and location of double bonds) facilitated the interpretation of the electron-density pattern of vitamin B_{12} itself, and the combination of *X*-ray and chemical evidence allowed the complete structural formula (VII) to be advanced for the vitamin.[3,6] The electron-density patterns reveal that an exchange reaction occurs during the formation of the hexacarboxylic acid since the cyanide group in the acid occupies the same position relative to the rest of the molcule as does the benziminazole residue in the vitamin. The aminopropanol which is linked ester-wise to the phosphate and through an amide linkage to the central portion of the molecule [9] is found to be attached to the propionic acid side-chain of ring D. The vitamin is formulated as a diester of phosphoric acid, the remaining acid group of the phosphate being neutralised by a positive charge associated with the cobalt atom. This accords with the stability of the phosphate

[5] Kaczka, Wolf, and Folkers, *J. Amer. Chem. Soc.*, 1949, **71**, 1514.
[6] Bonnett, Cannon, Johnson, Sutherland, Todd, and Smith, *Nature*, 1955, **176**, 328.
[7] Kuehl, Shunk, and Folkers, *J. Amer. Chem. Soc.*, 1955, **77**, 251.
[8] Kuehl, Shunk, Moore, and Folkers, *ibid.*, p. 4418.
[9] Buchanan, Johnson, Mills, and Todd, *J.*, 1950, 426.

ester linkages, which excludes the possibility of a triester grouping,[10] and also with the properties of Factor B (vitamin B_{12} lacking only the nucleotide) which, in contrast to the vitamin, behaves electrophoretically as a monoacid base.[1]

The evidence so far presented does not permit any definite conclusion regarding the degree of unsaturation in either the hexacarboxylic acid or the vitamin. Structures (IV) and (VII) each contain five double bonds in conjugation although their location is different in the two cases but, in this sense only, they are tentative. That a conjugated system is present is certain from the absorption spectra and there is no reason to believe that it differs in extent in the two compounds. Although a system of six conjugated double bonds [*i.e.*, that in (VII) extended by a double bond between $C_{(7)}$ and $C_{(8)}$] has many attractions, not the least being that it would have two resonance forms making all the nitrogen atoms surrounding the cobalt equivalent, yet the five-double-bond system was suggested provisionally on the following grounds. From the first detailed *X*-ray patterns there appeared to be some departure from planarity in the neighbourhood of one nitrogen atom, and chlorination studies on vitamin B_{12} appeared to show that the vitamin reacted with 3 mols. of chloramine-T to give a product which contained only two atoms of chlorine and with a visible spectrum displaced towards the red.[11] The halogenation evidence seemed most readily explained by assuming that extension of the conjugated system had occurred by elimination of one mol. of hydrogen chloride from a halogenated derivative. This explanation would be feasible only on a structure containing five double bonds. There was, however, some doubt as to its validity since in the halogenation studies no pure compounds were isolated and the shift in absorption spectrum, although marked, might conceivably have some other explanation. Moreover, later *X*-ray evidence, although not decisive, tended to favour structures containing six double bonds. In view of these uncertainties it was clearly necessary to study the halogenation of the vitamin in more detail. This study is described in the following paper, together with an investigation of reactions leading to the formation of the lactam ring which occurs in the hexacarboxylic acid: it leads in fact to a preference for the structure with six double bonds.

Experimental

Vitamin B_{12}.—A sample was analysed (Found, in a sample dried to constant wt. at 80°/vac.: C, 55·4; H, 6·7; N, 14·2. Calc. for $C_{63}H_{90}O_{14}N_{14}PCo$: C, 55·8; H, 6·7; N, 14·5. Calc. for $C_{63}H_{88}O_{14}N_{14}PCo$: C, 55·8; H, 6·55; N, 14·5%).

Alkaline Hydrolysis of Vitamin B_{12}.—Crystalline vitamin B_{12} (air-dried; 2 g.) was dissolved in water (100 c.c.), and "AnalaR" sodium hydroxide (30 g.) was added. A quantity of a brown flocculent material separated and the mixture was heated under reflux (oil-bath temp., 145—150°) for 1 hr. The resulting brown solution became red on cooling, and it was then acidified with 17% hydrochloric acid (140 c.c.), diluted with water (400 c.c.), and shaken with phenol (4 × 100 c.c.) until the aqueous phase was colourless. The combined phenolic extracts were washed with water (2 × 200 c.c.), any coloured material in the resulting aqueous layer being re-extracted into phenol. The combined salt-free phenol solution was diluted with three volumes of ether and then shaken with 0·2N-aqueous ammonia until no more colour was removed from the organic layer. The cobalt-containing acids and the nucleotide were thus obtained in the aqueous layer as their ammonium salts. A small quantity of a reddish-purple compound remained in the ethereal solution. After washing and evaporation of the ether and removal of phenol from the residue, the product was obtained as an amorphous solid (68 mg. from several experiments using a total of 10·99 g. of vitamin B_{12}) which has not yet been induced to crystallise; it is apparently cobalt-free (no blue borax bead; no residue after ignition) and has not been identified. The compound is insoluble in light petroleum or water but soluble in aqueous alkali or chloroform to bright reddish-purple solutions.

The aqueous solution of the ammonium salts of the cobalt-containing acids from several experiments (10·99 g. of vitamin B_{12}) was washed with ether and evaporated under reduced

[10] Brown, Magrath, and Todd, *J.*, 1955, 4396.

[11] Ellis, Petrow, Beaven, and Holiday, *J. Pharm. Pharmacol.*, 1953, **6**, 60; Schmid, Ebnöther, and Karrer, *Helv. Chim. Acta*, 1953, **36**, 65.

XUM

pressure. A blue colour obtained in the distillate was probably due to traces of indophenol formed by the interaction of phenol and ammonia. The last traces of water were removed from the non-volatile residue by freeze-drying, leaving a dark red resin (11·325 g.). Examination of this product by electrophoresis on paper (0·1M-potassium cyanide on Whatman No. 4 paper with 4·6 v/cm. for 5 hr.; Part III, *loc. cit.*) revealed the presence of tetra-, penta-, and hexa-carboxylic acids lacking the nucleotide, as well as the free nucleotide.

The product was initially subjected to analysis by ion-exchange chromatography on a column (1 × 12 cm.) of Dowex 1 × 2 resin (through 200 mesh) in the chloride form. The hydrolysate (8 mg.) in water (0·5 c.c.) was treated with 2% aqueous hydrogen cyanide (2 c.c.), brought on to the column with 0·02% aqueous hydrogen cyanide (20 c.c.), and eluted with acetic acid (0·05N containing 0·02% of hydrogen cyanide). The flow was adjusted to 1·3 c.c./min. and fractions (10 c.c.) of the eluate were examined spectroscopically. Measurements of the optical density at 277 mμ showed that the nucleotide was eluted rapidly (fractions 2—6) together with a small quantity of coloured material. The further examination of the nucleotide will be described in a later paper. After 15 fractions had been collected the column was washed with 0·02% aqueous hydrogen cyanide (40 c.c.) and then eluted with 0·3M-sodium chloride containing 0·02% of hydrogen cyanide. Optical-density measurements were now taken at 364 mμ and three peaks were obtained in the fraction-number (fractions counted after introduction of sodium chloride solution)–optical-density graph, *viz.*: fraction 16 (tetracarboxylic acid as determined by electrophoresis); fraction 27 (pentacarboxylic acid); and fraction 50 (hexacarboxylic acid). Area measurements on the graph showed that the ratio of tetra- : penta- : hexa-carboxylic acid was 1 : 11 : 22. This technique was the basis of the large-scale separation of the cobalt-containing acids.

Separation of Cobalt-containing Acids by means of Ion-exchange Chromatography. Use of Dowex 1 × 2 Chloride and Aqueous Sodium Chloride for Elution.—The mixed hydrolysate (6·021 g. as ammonium salts from previous experiment) was dissolved in 0·8% aqueous hydrogen cyanide (100 c.c.) and added to a column (23 × 6·5 cm.) of Dowex 1 × 2 in the chloride form (50—100 mesh) and washed with 0·02% aqueous hydrogen cyanide (200 c.c.). The 5 : 6-dimethylbenziminazole nucleotide was eluted with 0·05N-acetic acid (1800 c.c.) containing 0·02% of hydrogen cyanide, and the column washed with 0·02% aqueous hydrogen cyanide (150 c.c.), followed by 0·3M-sodium chloride containing 0·02% of hydrogen cyanide, adjusted to flow at the rate of 17·4 c.c./min. The first runnings (1500 c.c.) were discarded and thereafter fractions (1 l. each) collected, the concentration of salt solution being slowly increased as shown in Table 1. A small portion of each fraction was extracted and concentrated by the phenol–ether method as outlined in the previous experiment and then subjected to electrophoresis on paper. Fractions 1—8 inclusive were purple (most intense in fraction 6), and fraction 9 was orange-brown.

Fraction 9, and to a smaller extent fraction 8, showed a yellowish spot in the pentabasic acid region after electrophoresis and an orange-purple spot in the hexabasic acid region. These are included in square brackets in Table 1.

TABLE 1.

Fraction	1	2	3	4	5	6	7	8	9
Normality of NaCl eluting soln.	0·3	0·3	0·3	0·4	0·4	0·6	0·6	1·0	1·0
No. of CO_2H in constituent acids (electrophoresis)	4, 5	5	5	5	5, 6	6	6	6[5, 6]	[5, 6]

A similar experiment with a mixed hydrolysate (5·304 g.) was carried out and the corresponding chromatography fractions were combined. Evaporation of the acetic acid solution yielded the 5 : 6-dimethylbenziminazole nucleotide (2·205 g. from 10·99 g. of vitamin B_{12}) as a dirty white amorphous solid [R_F 0·51 in a butan-1-ol–acetic acid–water (4 : 1 : 5); lit.,[9] 0·48]. The coloured fractions 1—9 were extracted by the phenol–ether method and combined as follows: fraction 1 (0·178 g.; free acid); fractions 2—5 (1·973 g.; ammonium salt); fractions 6—8 (5·492 g.; ammonium salt); and fraction 9 (0·159 g.; free acid). Each of these combined fractions was subjected to further purification.

Fractions 6—8 were combined and chromatographed on an ion-exchange column (23 × 6·5 cm.; 50—100 mesh), elution being with aqueous 0·3M-sodium chloride containing 0·02% of hydrogen cyanide. There were obtained (i) homogeneous (electrophoresis) hexacarboxylic acid (4·479 g.), (ii) mixed ammonium penta- and hexa-carboxylates (225 mg.) which were combined with fractions 2—5 (below), and (iii) tail fraction (245 mg.).

XUM

Fractions 2—5 (2·198 g. as ammonium salt) were combined and chromatographed as above and yielded (i) homogeneous (electrophoresis) pentacarboxylic acid (0·766 g.), (ii) a mixture (64 mg.) of tetra- and penta-carboxylic acids which was combined with fraction 1 (below), and (iii) mixed ammonium salts (1·023 g.) of the penta- and hexa-carboxylic acids. Fraction (iii) was again chromatographed on a column (2·5 × 11 cm.) of Dowex 1 × 2 (200-mesh; chloride form), and eluted with 0·3M-sodium chloride containing 0·02% of hydrogen cyanide at a rate of 2·2 c.c./min., 10 c.c. fractions being collected. This gave pure (electrophoresis) pentacarboxylic acid (672 mg.), hexacarboxylic acid (252 mg.), and a small amount of the mixture (57 mg.).

Fraction 1 (242 mg.) was subjected to further fractionation on a small ion-exchange column (2·5 × 11 cm.), and the various fractions were isolated as before. There were obtained pure (electrophoresis) tetracarboxylic acid (49 mg.), pure pentacarboxylic acid (147 mg.), and a mixture of tetra- and penta-carboxylic acids (31·5 mg.).

The overall yields of the pure acids were : tetracarboxylic 49 mg., pentacarboxylic 1·585 g., and hexacarboxylic 4·731 g.

Crystalline Dicyanide Derivative of the Pentacarboxylic Acid.—Electrophoretically homogeneous pentacarboxylic acid (500 mg.; previous experiment) was dissolved in the minimum amount of hot 50% aqueous acetone, and 4% aqueous hydrogen cyanide (5 c.c.) was added. The solution was cooled slowly and then kept at 0° for several days, then the dark red needles were separated and washed with a little water, both operations being conducted in subdued light. After a second crystallisation by the same method the crystalline *dicyanide* (240 mg.) was dried at 50°/0·05 mm. (Found, in a sample dried to constant wt. : C, 57·3; H, 6·3; N, 10·8. $C_{47}H_{59}O_{12}N_8Co$ requires C, 57·2; H, 6·0; N, 11·35. $C_{47}H_{61}O_{12}N_8Co$ requires C, 57·1; H, 6·2; N, 11·3%). Light absorption : (i) in H_2O, max. at 530, 500, 402, 353, 318—319, 223—224 mμ (log ε 3·86, 3·86, 3·59, 4·36, 3·95, 4·49 respectively); (ii) in 0·1M-KCN, max. at 579—580, 540, 413, 365, 348, 312, 302, 276, 215 mμ (log ε 3·94, 3·91, 3·30, 4·43, 4·14, 3·93, 3·91, 3·96, 4·50 respectively); (iii) in 0·1N-NaOH, max. at 576—577, 540—541, 412—413, 364, 312, and 276 mμ (log ε 3·85, 3·91, 3·34, 4·39, 3·92, 3·93, respectively). The infrared spectrum (Nujol mull) showed max. at 2119, 1709, 1695, 1580, 1504, 1399, 1304, 1258, 1185, 1160, 1143, 1120, 1058, 1047, 1021, 987, 973, and 946 $cm.^{-1}$. On the analytical ion-exchange column, the pentacarboxylic was obtained as a single band in tubes 20—25; on paper with butan-1-ol–acetic acid–2% hydrogen cyanide (4 : 1 : 5) it was obtained as a slightly elongated spot, R_F 0·62. On electrophoresis on Whatman No. 4 paper under standard conditions (0·1M-potassium cyanide solution for 5 hr. at 4·6 v/cm.) the pentacarboxylic acid migrated 10·1 cm. The acid did not melt below 300°; it was very soluble in aqueous acetone, phenol, and alkali, soluble in water, and insoluble in acetone or ether.

Crystalline Dicyanide Derivative of the Hexacarboxylic Acid.—Electrophoretically homogeneous hexacarboxylic acid was crystallised from aqueous acetone containing hydrogen cyanide as described for the pentacarboxylic acid, giving a *dicyanide* (Found, in a sample dried to constant wt. : C, 56·7; H, 6·0; N, 9·7. $C_{47}H_{58}O_{13}N_7Co$ requires C, 57·1; H, 5·9; N, 9·9. $C_{47}H_{60}O_{13}N_7Co$ requires C, 57·0; H, 6·1; N, 9·9%). Light absorption : (i) in H_2O, max. at 528, 497, 402, 380, 350—352, 318, 220—226 mμ (log ε 3·88, 3·91, 3·62, 3·62, 4·39, 3·99, 4·53 respectively); (ii) in 0·1M-KCN, max. at 576—577, 537, 412, 363, 348, 311, 301, 276, 212 mμ (log ε 3·97, 3·94, 3·32, 4·48, 4·16, 3·96, 3·92, 3·97, 4·62 respectively); (iii) in 0·1N-NaOH, max. at 532—539, 410—411, 360, 312—314, 275—276 mμ (log ε 3·91, 3·46, 4·34, 3·96, 3·99 respectively). The infrared spectrum (Nujol mull) showed max. at 2119, 1715, 1686, 1610, 1587, 1504, 1416, 1399, 1290, 1232, 1205, 1190, 1163, 1153, 1111, 1093, 1058, 1042, 1019, 1006, 974, and 810 $cm.^{-1}$. On the analytical ion-exchange column, the hexacarboxylic acid was obtained as a single band in tubes 44—50; on paper with the butan-1-ol–acetic acid–2% hydrogen cyanide it was obtained as a slightly elongated spot, R_F 0·76. Under standardised electrophoresis conditions (see under pentacarboxylic acid) it moved 11·7 cm. The solubilities of the hexacarboxylic acid in various solvents were similar to those of the pentacarboxylic acid.

Purification of Cobalt-containing Acids by means of Ion-exchange Chromatography. Use of Dowex 1 × 2 Acetate and Aqueous Ammonium Acetate for Elution.—A column of Dowex 1 × 2 acetate (18 × 2·5 cm.) was prepared and an aqueous solution (26 c.c.) of the ammonium salt of the hexabasic acid (490 mg.; obtained by electrophoresis on Whatman "seed-test" paper; Part III, *loc. cit.*) brought on to it. After being washed with water (100 c.c.) the column was developed with 0·5M-aqueous ammonium acetate until 3200 c.c. of eluate had been collected. A broad red band travelled slowly down the column and several minor bands were included in

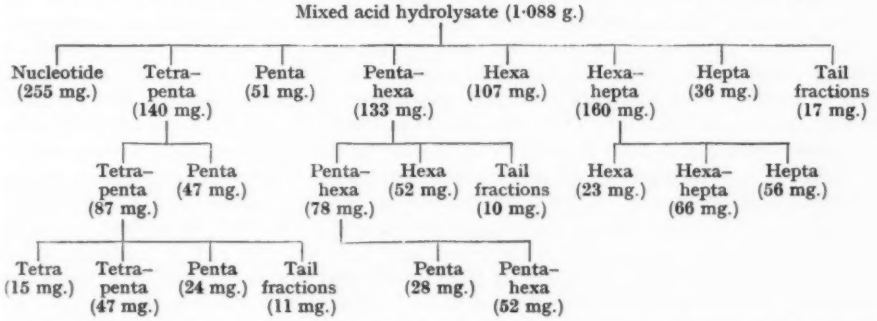
the eluate. Elution was continued with 0·6M-ammonium acetate, two major red fractions being obtained. The second and larger of these, obtained after 3200 c.c. of eluate had been collected, was acidified to pH 2 with concentrated hydrochloric acid and extracted with phenol. The phenolic extract was washed with N-hydrochloric acid to remove ammonium salts, and with water to remove chloride ions, then diluted with ether (3 vols.). The hexabasic acid was extracted with water, and the aqueous solution evaporated to dryness under reduced pressure. The red gum obtained was dissolved in water (7 c.c.), and acetone (100 c.c.) was added. Ether was added until a faint turbidity was produced and the solution was set aside for several weeks. The dark red prisms which separated were removed and sent to Dr. Hodgkin for *X*-ray crystallographic examination. The filtrate was again evaporated to dryness, the residue dissolved in aqueous acetone (1 : 4; 2 c.c.), and acetone (20 c.c.) added. After separation of a little amorphous material, ether was added to the solution until a turbidity was produced and, after scratching, fine red needles (130 mg.) of the *hexabasic acid* were deposited (Found, in material dried to constant wt. at 54°/0·05 mm.: C, 52·8; H, 6·3; N, 7·85. $C_{46}H_{60}O_{13}N_6CoCl,2H_2O$ requires C, 53·2; H, 6·2; N, 8·1. $C_{46}H_{58}O_{13}N_6CoCl,2H_2O$ requires C, 53·5; H, 6·05; N, 8·1%). Light absorption: (i) in H_2O, max. at 528, 497, 402, 380—381, 350, and 317 mμ (log ε, 3·90, 3·92, 3·62, 3·59, 4·42, and 4·02 respectively) with an inflection at 264—270 mμ (log ε 4·34); (ii) in 0·1M-KCN, max. at 576, 537, 411, 363, 347, 311, 302, 287, and 277 mμ (log ε 3·97, 3·94, 3·29, 4·50, 4·18, 3·97, 3·93, 3·81, and 3·99 respectively). The infrared spectrum, determined on a mull in Nujol, showed max. at 2141, 2114, 1733, 1709, 1664, 1626, 1587, 1506, 1292, 1157, 1114, 1093, 1064, 1049, 1015, 976, and 813 $cm.^{-1}$.

A solution of the crystalline hexabasic acid (needles; 2·1 mg.) in 0·01N-ammonia was put on a column of Dowex 1 × 2 sulphate (9·5 × 1 cm.), washed with water, and eluted with 0·1M-sodium sulphate. Fractions (10 c.c.) of the eluate were collected and the intensity of light absorption at 351 mμ of each fraction was determined. Two main fractions were thus obtained, suggesting that some sulphate had been introduced into the molecule.

Acid Hydrolysis of Vitamin B_{12}.—Vitamin B_{12} (1·08 g.; air-dried) was dissolved in 2N-hydrochloric acid (50 c.c.) and heated in a boiling-water bath for 2 hr. The product was cooled and extracted by the phenol–ether method as described for the alkaline hydrolysate of vitamin B_{12} (above). From the aqueous solution there were obtained the combined ammonium salts (1·085 g.) of the mixed cobalt-containing acids and the nucleotide, and from the ethereal layer a small quantity of a crimson amorphous material (9·8 mg.).

The method of separation employed was similar to that described above for use with the alkaline hydrolysate. An examination of a small fraction of the product by the analytical Dowex 1 × 2 column showed that the nucleotide could be separated from the cobalt-containing acids and that these consisted of a mixture of tetra-, penta-, hexa-, and hepta-carboxylic acids in the approximate ratio, 1 : 6 : 9·5 : 4·5. These acids were eluted from the column in the same relative order as the acids obtained from the alkaline hydrolysis but the heptacarboxylic acid required 0·4M-sodium chloride for elution.

TABLE 2. *Ion-exchange separation of the acid hydrolysate from vitamin B_{12}.*



For the large-scale separation a column (10 × 2·5 cm.) of Dowex 1 × 2 (through 200 mesh) in the chloride form was used with a flow rate of 2·15—2·9 c.c./min. The experiment was conducted as before and 10 c.c. fractions were collected. Every tenth fraction was examined

by electrophoresis and the progress of the separation is illustrated in Table 2. The various tail fractions were not examined further; they contained material which could not be separated cleanly by electrophoresis. The combined yields of electrophoretically homogeneous material were: tetracarboxylic acid 15 mg.; pentacarboxylic acid 150 mg.; hexacarboxylic acid 182 mg.; heptacarboxylic acid 92 mg.; and nucleotide, 255 mg. containing a small amount of nucleoside.

We are deeply indebted to Glaxo Laboratories Limited for generously making available to us supplies of vitamin B_{12} throughout these investigations. Gifts of crystalline vitamin from Lederle Laboratories Inc. and Chas. Pfizer and Co. Inc. are also gratefully acknowledged. We thank Dr. W. Zimmermann of C.S.I.R.O. Melbourne for microanalyses, the Beit Memorial Trustees for a Fellowship (to J. R. C.), and the D.S.I.R. for a Maintenance Allowance (to R. B.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 12th,* 1956.]

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227. *Chemistry of the Vitamin B_{12} Group. Part V.* The Structure of the Chromophoric Grouping.*

By R. BONNETT, J. R. CANNON, V. M. CLARK, A. W. JOHNSON, L. F. J. PARKER, E. LESTER SMITH, and SIR ALEXANDER TODD.

Structures for vitamin B_{12} (I) and its hexacarboxylic acid degradation product (II) containing six rather than five conjugated double bonds are adopted and reactions bearing on this point are considered. With mild alkali in the presence of oxygen the acetamide side-chain of ring B of the vitamin undergoes cyclisation, to give dehydrovitamin B_{12}, a γ-lactam, whereas with an equivalent of a halogenating agent the same side-chain is converted into a γ-lactone; mechanisms for these cyclisations are considered. The reaction of vitamin B_{12} with more than one equivalent of halogenating agent has a marked effect on the chromophore; under analogous conditions, dehydrovitamin B_{12} gives a crystalline monohalogeno-derivative.

IN the preceding paper structural formulæ were presented for vitamin B_{12} and for the crystalline nucleotide-free hexacarboxylic acid obtained from it by treatment with 30% aqueous sodium hydroxide at 150°; both compounds were represented as containing five conjugated double bonds but it was emphasised that available evidence did not really permit of any clear decision between this degree of unsaturation and a system of six conjugated double bonds, the extended system having, indeed, certain attractions. It was hoped to reach a final decision by studying in detail the halogenation of the vitamin and some of its degradation products. This has now been achieved and we conclude that vitamin B_{12} and the hexacarboxylic acid degradation product each contain six conjugated double bonds. The same conclusion has been reached on *X*-ray crystallographic evidence.[1] They are therefore represented by structures (I) and (II) respectively, the conjugated system being shown arbitrarily in two alternative resonance forms. The chemical evidence upon which this conclusion rests comes primarily from halogenation experiments, but before dealing with these it is desirable to consider the formation of the lactam ring in the acid (II). Hydrolysis of all seven amide linkages in vitamin B_{12} to give a hepta-carboxylic acid occurs only under acidic conditions; under alkaline conditions no hepta-carboxylic acid is produced and the hexacarboxylic acid (II) is the end product. Clearly the formation of the lactam ring in this must have been the result of an oxidation at an early stage in the alkaline treatment of the vitamin and it is noteworthy that there are four positions (starred) in formula (I) which are " activated " by carbon–nitrogen double bonds.

* Part IV, preceding paper.

[1] Hodgkin, Kamper, Mackay, Pickworth, Trueblood, and White, *Nature*, 1956, **178**, 64.

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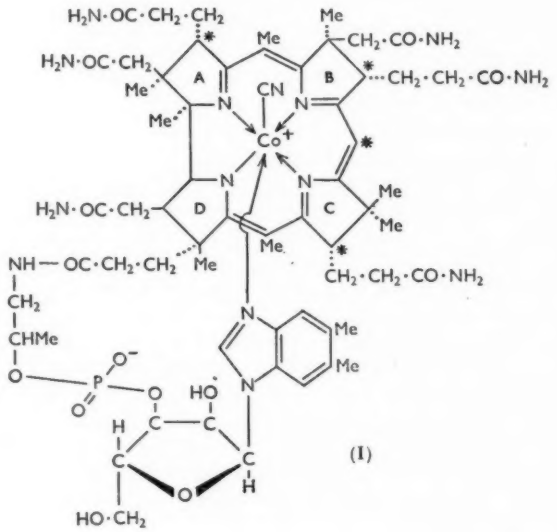
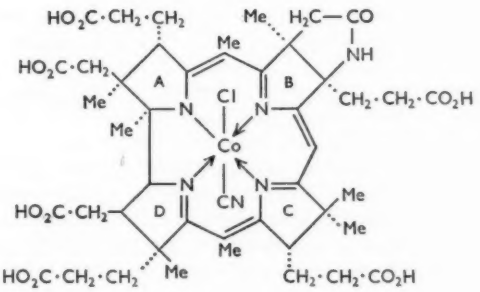
In our preliminary communication [2] we suggested tentatively that cyclisation of the acetamide residue in ring B was preceded by hydroxylation at the β-position of the ring and involved dehydration or an equivalent reaction. This suggestion followed on our opinion that the neutral crystalline compound formed by aerial oxidation of vitamin B_{12} under mild alkaline conditions [3] was a monohydroxy-derivative of the vitamin. These views now require modification.

The oxidation product is very similar to vitamin B_{12} in its physical properties, *e.g.*, spectra, electrophoretic and chromatographic behaviour, but it is almost devoid of



(I)



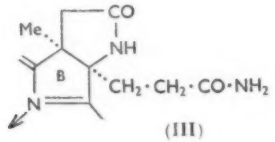
(II)

biological activity. Vigorous acidic hydrolysis of the oxidation product yields penta- and hexa-carboxylic acids but no hepta-carboxylic acid. Treatment of the oxidation product in the cold with alkali yields various acids formed by hydrolysis of amide groups; these are different from the corresponding acids obtained from the vitamin [4] and reconversion of the monocarboxylic acid fraction into the corresponding amide gives a biologically

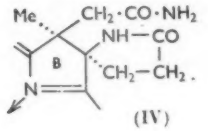
[2] Bonnett, Cannon, Johnson, Sutherland, Todd, and Smith, *ibid.*, 1955, **176**, 328; Hodgkin, Johnson, and Todd, *Chem. Soc. Special Publ. No.* 3, 1955, p. 109.
[3] Lester Smith, *Biochemical Soc. Symp.*, No. 13, 1955, p. 12.
[4] Armitage, Cannon, Johnson, Lester Smith, Parker, Stafford, and Todd, *J.*, 1953, 3849.

inactive oxidation product. Vigorous alkaline hydrolysis ultimately yields a hexacarboxylic acid which appears to be identical with the acid (II).

These results suggest that formation of the oxidation product in alkaline solution has involved direct cyclisation to yield the lactam (as in II) rather than hydroxylation at one of the starred positions in (I). Members of the chlorin series of chlorophyll derivatives are known to undergo hydroxylation at equivalent positions in the reduced ring,[5] but it is doubtful whether cyclisation of a hydroxyvitamin B_{12} would occur under the experimental conditions. Further examination has confirmed that a lactam ring is present in the oxid-

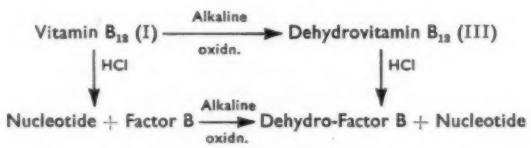


(III)



(IV)

ation product which can be described as dehydrovitamin B_{12}. For convenience the dehydrovitamin is represented by the partial structure (III); only ring B is shown since the molecule is otherwise identical with vitamin B_{12} (I). The alternative structure (IV) is much less likely since it has been established by *X*-ray methods [6] that the hexacarboxylic acid (II), obtained by vigorous alkaline hydrolysis of the vitamin, contains the lactam grouping shown in (III) and the dehydrovitamin is almost certainly an intermediate in its production. The intensity of absorption at 1710 cm.$^{-1}$ in the infrared spectrum of the dehydrovitamin is increased relatively to that of vitamin B_{12}, and this is consistent with the formation of a γ-lactam as in (III) [cf. the hexacarboxylic acid (II) which shows a band at 1720 cm.$^{-1}$]. The dehydrovitamin is unaffected at 130° under reduced pressure. By short heating at 60° with concentrated hydrochloric acid the nucleotide is removed, giving a non-crystalline but homogeneous substance analogous to Factor B (obtained from vitamin B_{12} by similar treatment) but distinguishable from it both by chromatography and by microbiological assay. The same product is obtained by aerial alkaline oxidation of Factor B itself.



When the mixture of the three monocarboxylic acids obtained [4] by mild acidic hydrolysis of vitamin B_{12} is subjected to aerial alkaline oxidation and the products are examined electrophoretically at various pH's, no lactonic material can be detected. The known difference [7] in the rates of hydrolysis of γ-substituted as compared with β-substituted amides ($\gamma \gg \beta$) permits the assumption that the monocarboxylic acids obtained from the vitamin are isomers with one propionic acid residue on rings A, B, and C respectively. The above findings therefore argue against the presence of a free hydroxyl group in the β-position of one of these rings in the product of aerial alkaline oxidation and strongly support our thesis that partial structure (III) represents dehydrovitamin B_{12}.

The pronounced colour changes which are observed in presence of insufficient oxidising agent both in the vigorous alkaline hydrolysis of the vitamin (red ⟶ dark brown ⟶ red) and its mild alkaline oxidation (red ⟶ brown ⟶ red) strongly suggest that the cobalt

[5] Fischer *et al.*, *Annalen*, 1941, **547**, 234; 1943, **555**, 81.
[6] Hodgkin, Pickworth, Robertson, Trueblood, Prosen, and White, *Nature*, 1955, **176**, 325.
[7] Cason and Wolfhagen, *J. Org. Chem.*, 1949, **14**, 155; Cason, Castaldo, Clusker, Allinger, and Ash, *ibid.*, 1953, **18**, 1129.

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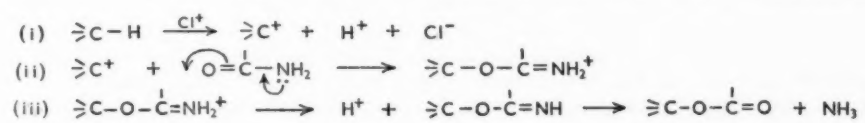
atom is involved in the initial phase of reaction in which oxidation occurs at the activated position on ring B. This is supported by the observation that the reaction both with vitamin B_{12} and Factor B is retarded by sodium mercaptoacetate and prevented by cyanide ions which stabilise the tervalent cobalt complex; this prevention of reaction recalls the inhibition of oxygen transfer on addition of cyanide to hæmoglobin.

The mechanism of the reaction is as yet unknown but would seem to be a one-electron oxidation involving formation of a radical at the starred position in ring B with simultaneous reduction of the cobalt from the tervalent to the bivalent state. The radical would then react with the acetamido-group to yield a lactam.

Knowledge of the nature and mode of formation of dehydrovitamin B_{12} is of value in understanding the reaction between vitamin B_{12} and halogenating agents. It has been reported [8] that *N*-chloroamides react with the vitamin and that three equivalents of the reagent are consumed before a product is obtained which is relatively stable in the presence of an excess of it. The product, although apparently micro-crystalline, was recognised as a mixture; analysis indicated that the halogen content corresponded to the introduction of two chlorine atoms into the molecule and, in the dicyanide form, the product appeared blue rather than red. Our early experiments showed that the normal Carius method for halogen analysis was unreliable in the B_{12} series and we developed a direct combustion technique in which the material was burned in a stream of oxygen and the halogen so produced estimated as halide ion after absorption in alkaline hydrogen peroxide.[9]

Subsequently, the reaction of the vitamin with halogens has been studied more closely. When treated with one equivalent of chloramine-T, vitamin B_{12} is converted into a red crystalline substance which is biologically inactive when assayed with *L. leichmannii*, *E. coli*, or *Ochromonas malhemensis*, and contains no halogen. The same product is obtained by the action of 1 equivalent of bromine water at pH 4 or by iodine in alkaline solution although in the latter case it is accompanied by dehydrovitamin B_{12} (III). [The lactam (III) is, indeed, the major product when the iodine concentration is low.]

This new substance is not isomorphous with the vitamin, and mixtures of the two can be separated by fractional crystallisation. It behaves as a neutral substance on electrophoresis at pH 6·5, but as a monobasic acid after treatment with aqueous sodium hydroxide for a few minutes. This change from a neutral to an acidic substance is reversible and strongly suggests that the halogenation product is a lactone. Both the neutral product and the acid into which it can be converted have been obtained crystalline and their absorption spectra confirm the postulated lactone–acid relationship. The infrared spectrum of the acidic form is very similar to that of vitamin B_{12} but that of the neutral form shows a new band at 1783 cm.$^{-1}$ which is consistent with the presence of a saturated γ-lactone group; the ultraviolet and visible spectra of the two forms are very similar to those of vitamin B_{12}, the principal bands being at 360 and 550 mμ for the acid and 359 and 552 mμ for the neutral form. The formation of this lactone evidently involves one of the amide groups in vitamin B_{12} since ammonia is also a product of the reaction and the lactone contains one nitrogen atom less than the vitamin. We interpret the course of



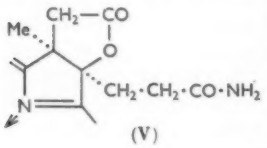
reaction as involving oxidation of one of the activated β-positions in (I) followed by reaction of the carbonium ion with the carbonyl-oxygen atom of the amide.[10] The sequence of

[8] Ellis, Petrow, Beaven, and Holiday, *J. Pharm. Pharmacol.*, 1953, **6**, 60; Schmid, Ebnöther, and Karrer, *Helv. Chim. Acta*, 1953, **36**, 65.
[9] Perold, *S. African Ind. Chemist*, 1953, **7**, 96.
[10] Winstein and Boschan, *J. Amer. Chem. Soc.*, 1950, **72**, 4669.

reactions is indicated on p. 1161; steps (ii) and (iii) are analogous to the reaction of acid halides with amides leading ultimately to anhydrides.[11]

All available evidence supports the view that the initial point of attack by the halogen is in ring B and that the lactone is a structural analogue of dehydrovitamin B_{12} (III), *i.e.*, that it has the partial structure (V).

The lactone can be recovered after treatment with hot dilute alkali under conditions used for the preparation of dehydrovitamin B_{12}, and when it is subjected to vigorous alkaline hydrolysis under the conditions which yield the hexacarboxylic acid (II) from vitamin B_{12} it yields a heptacarboxylic as well as a hexacarboxylic acid fraction. This is the only known instance of the formation of a heptacarboxylic acid by alkaline hydrolysis of a vitamin B_{12} derivative. These results not only accord with the lactone formulation but indicate with a high degree of probability that the formation of the lactone has blocked the position in ring B which is involved in lactam formation during the alkaline treatment discussed earlier. Furthermore, when dehydrovitamin B_{12} (III) is treated with one equivalent of halogenating agent it does not give a lactone; instead it is partly unchanged and partly converted into a new product which gives a blue cyanide derivative as does vitamin B_{12} after treatment with more than one equivalent of halogenating agent. Our preference for partial structure (V) is based on our choice of (III) rather than (IV) for dehydrovitamin B_{12}. Similar halogenation of two of the isolated isomeric monocarboxylic acids obtained [2] by mild hydrolysis of vitamin B_{12}, as well as of a mixture of all three isomers, yields in each instance lactonic acids, *i.e.*, the free acid groupings (one of which was almost certainly the propionic acid group on ring B) were not involved in the lactonisation. The lactone (V) was converted into derivatives of Factor B by warming it with concentrated hydrochloric acid for a short time. Although crystalline products were not isolated the nucleotide was removed and a neutral product (presumably the lactone derivative of Factor B) was produced together with mono- and di-basic acids formed by further hydrolysis of amide groups; all these products retained the lactone group, as shown by their electrophoretic behaviour before and after alkaline treatment.



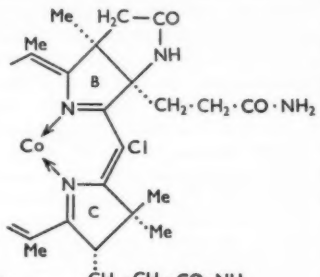
(V)

Whereas treatment with one equivalent of a halogenating agent has little effect on the ultraviolet and visible absorption of vitamin B_{12} (see above), addition of a second equivalent causes a marked bathochromic shift; during this reaction displacement of cyanide ion from the co-ordination shell may occur but this alone would result in a hypsochromic shift. In aqueous solution the bands at 361 and 550 mμ are displaced to 364 and 580 mμ, and in aqueous potassium cyanide (*i.e.*, as dicyanide) the bands at 368, 540, and 581 mμ are displaced to 370, 572, and 612 mμ respectively. Similar shifts in spectra are obtained when dehydrovitamin B_{12} (III) is treated with one equivalent of halogenating agent. Clearly it is only after the starred β-position in ring B is blocked (*e.g.*, by lactam or lactone formation) that attack by halogen seriously affects the chromophore. It was the pronounced bathochromic effect of halogenation that led us originally to favour a structure for vitamin B_{12} containing five conjugated double bonds (cf. Part IV); the magnitude of the shift suggested an increase in conjugation from five to six double bonds, which, if it were brought about by elimination of one mol. of hydrogen halide, would account for the apparent presence of only two chlorine atoms in the products of chlorination of the vitamin with three equivalents of halogen. The isolation of the lactone (V) as the halogen-free initial product in the halogenation reaction and our appreciation of the unreliable character of previous halogen analyses clearly undermined this argument and it became important to isolate the products of more extensive halogenation.

With dehydrovitamin B_{12} a bathochromic shift is apparent immediately upon introduction of the halogenating agent and, by using 1 mol. of chloramine-T, it is possible

[11] Titherley, *J.*, 1904, **85**, 1673.

to isolate a crystalline compound which contains one atom of chlorine and has lost the co-ordinated cyanide ion. The same monochloro-compound is obtained on using two and five mols. of chloramine-T. The action of excess of halogenating agent on vitamin B_{12} itself gives an amorphous halogen-containing lactonic product having spectral characteristics similar to those of the crystalline monochlorodehydrovitamin B_{12}, absorption bands being observed at 548 and 580 mμ in aqueous solution, whereas the vitamin has the corresponding bands at 520 and 550 mμ. From a consideration of electron-availability at the various positions in the chromophore [12] we presume that halogenation occurs at the free *meso*-position between rings B and C, to give the compound (VI), and the bathochromic shift is to be compared with that observed in passing from methyl vinyl ketone ($\lambda_{max.}$ 210 mμ) to methyl 2-chlorovinyl ketone ($\lambda_{max.}$ 228 mμ).[13]



(VI)

The behaviour of the hexacarboxylic acid (II) towards chloramine-T is complicated by decomposition accompanied by a rapid fall in light absorption; in this case, no pure chlorinated compound has been isolated.

We conclude that the chromophoric anion in vitamin B_{12}, dehydrovitamin B_{12}, and the hexacarboxylic acid is degenerate, the 13 atom system containing six double bonds, and that the bathochromic shifts on halogenation are attributable to substitution rather than extension of the chromophore. Our failure to dehydrogenate the chromophoric system in the esterified hexacarboxylic acid by hydrogen-transfer to chloranil [14] is in accord with this interpretation.

When vitamin B_{12} is treated with silver oxide in ethanol–pyridine under the conditions that bring about hydroxylation of the chlorophyll molecule,[15] the main product is the same lactone that is formed from vitamin B_{12} by reaction with limited amounts of halogens; a smaller amount of the lactam is also formed. The lactone is converted into three uncharacterised products by prolonged heating with silver oxide in ethanol–pyridine under reflux.

Experimental

Dehydrovitamin B_{12}.—A solution of vitamin B_{12} (528 mg.; hydrated crystals) in aqueous 0·1N-sodium hydroxide (105 c.c.) was heated at 100° for 10 min. while a brisk current of air was drawn through the solution. After cooling to room temperature, the brown solution was acidified with dilute hydrochloric acid, and the red product extracted with small volumes of phenol until all the colour was removed from the aqueous layer. The combined phenolic extracts were washed with a little water to remove chloride ions, then diluted with ether, and the red product re-extracted into a small volume of water. 2% Aqueous hydrogen cyanide solution (2 c.c.) was added to the red aqueous extract which was then concentrated (to 20 c.c.) under reduced pressure on the water-bath. The product was then applied to a column (14 × 1 cm.) of Dowex 1 × 2 (acetate form) and eluted with water, the neutral product being obtained in the eluate and the acidic products adsorbed on the column. The aqueous eluate was concentrated as before (to 10 c.c.) and acetone added until a faint turbidity was produced. The solution gradually deposited long red needles (272 mg.) of *dehydrovitamin B_{12}* (Found, after drying at 50° *in vacuo* for 3 days: C, 55·3; H, 6·6; N, 14·2. $C_{63}H_{86}O_{14}N_{14}PCo$ requires C, 55·9; H, 6·4; N, 14·5%). Light absorption: (i) in H_2O, max. at 548, 517, 408, 359, 320, 304, 278 mμ (log ε 3·81, 3·80, 3·45, 4·35, 3·80, 3·87, and 4·09 respectively); (ii) in 0·1M-KCN, max. at 581, 541, 415, 366, 313, 303, 288, 278 mμ (log ε 3·87, 3·83, 3·21, 4·36, 3·86, 3·83, 3·92, and 4·02

[12] Cf. Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 265, 275, 283.
[13] Bowden, Braude, and Jones, *J.*, 1946, 948.
[14] Braude, Jackman, and Linstead, *J.*, 1954, 3548.
[15] Fischer and Lautsch, *Annalen*, 1937, **528**, 247.

respectively), with inflections at 510 and 350 mμ (log ε 3·65 and 4·05). The infrared spectrum, determined in Nujol mull and as a potassium bromide plate, showed max. at 3350, 3155, 2920, 2140, 1670, 1580, 1507, 1387, 1370, 1215, 1146, and 875 cm.$^{-1}$. Dehydrovitamin B_{12} is indistinguishable chromatographically from vitamin B_{12} on paper when butan-1-ol–acetic acid–2% hydrogen cyanide (4 : 1 : 5) is used as solvent; but in butan-2-ol (1 l.) containing aqueous ammonia (*d* 0·88; 2 c.c.), 4% aqueous hydrogen cyanide (1 c.c.), and just sufficient water to saturate the system, it had R_F 1·15 relative to that of vitamin B_{12}. By the *E. coli* mutant plate assay a chromatographically pure sample of dehydrovitamin B_{12} showed 0·1—0·4% of the activity of vitamin B_{12}; it is impossible to be more precise because the response curves for the two substances have widely different slopes. The compound was inactive towards *Ochromonas malhemensis* and showed about 0·2% of the activity of vitamin B_{12} by the *Lactobacillus leichmannii* tube assay.

Prolonged Treatment of Vitamin B_{12} with Alkali.—Vitamin B_{12} (120 mg.; hydrated crystals) in 0·1N-aqueous sodium hydroxide (20 c.c.) was heated under reflux for 1 hr. The cooled solution was acidified and extracted with phenol as in the previous experiment. The final aqueous solution was applied to two sheets of Whatman seed-testing paper, as a streak *ca.* 20 cm. in length on each, and then submitted to electrophoresis in phosphate buffer (0·05N at pH 6·5, containing 0·01% of potassium cyanide) at 2·5 v/cm. for 16 hr. The papers showed a pattern of 5 red zones due to neutral products and mono- to tetra-basic acids, the mono- and di-basic acids being present in the largest amounts. Each of the red acidic zones was accompanied by a slightly faster-moving and partly overlapping purple zone due to the corresponding acid from which the nucleotide had been removed.[4] The zones were cut out separately as far as possible and the neutral and monobasic red fractions were submitted to electrophoresis in N-acetic acid at 4 v/cm. to remove remaining materials lacking the nucleotide.

The material which was neutral at pH 6·5 gave a main fraction (4·2 mg.), also neutral in acetic acid, and identical with the product obtained from brief treatment of vitamin B_{12} with alkali. The minor fraction was basic and gave an orange solution in acetic acid.

The red monobasic acids (8·1 mg.) were also purified by electrophoresis in acetic acid and then crystallised slowly from aqueous acetone. Chromatography on paper, solvent being butan-2-ol (1 l.) containing acetic acid (2 c.c.) and 4% aqueous hydrogen cyanide (10 c.c.), showed it to consist of a mixture of isomers, all different from those produced [4] by the action of cold dilute acids on vitamin B_{12} which were chromatographed on the same paper. The isomers from alkaline hydrolysis gave R_F values (relative to that of vitamin B_{12}) of 0·55 (weak), 0·95, and 1·3. The relative R_F values of those from acid hydrolysis were 1·2, 1·45, and 1·7 (weak).

Partial Synthesis of Dehydrovitamin B_{12}.—The monobasic acids (mixed isomers; 5 mg. of hydrated crystals) obtained in the foregoing experiment were dried at 120—130° under reduced pressure for 10 min. The dried material was dissolved in dry *NN*-dimethylformamide (0·15 c.c.) and triethylamine (0·015 c.c. of 20% v/v solution in dimethylformamide) was added, then cooled to −5°. Ethyl chloroformate (0·008 c.c. of 20% v/v solution in benzene) was added and the mixture kept at −5° for 15 min. It was then saturated with dry ammonia and kept for 3 hr. at room temperature. Acetone–ether (2 c.c.; 1 : 1) was added and the red precipitate separated and dissolved in a few drops of water. Examination of the solution by electrophoresis on Whatman 3MM paper showed that the main component was neutral. The *E. coli* mutant plate assay indicated 1·5—4% of the activity of the vitamin, confirming that the main product is dehydrovitamin B_{12} but containing a trace of the vitamin.

Treatment of Dehydrovitamin B_{12} with Concentrated Hydrochloric Acid.—(i) Dehydrovitamin B_{12} (5 mg.) was heated in concentrated hydrochloric acid at 65° for 4½ min. The acid was removed by evaporation under reduced pressure and the residue was chromatographed on Whatman 3MM paper in the acidic butan-2-ol system, alongside a similar hydrolysate of vitamin B_{12}, known to consist mainly of Factor B (vitamin B_{12} lacking the nucleotide) and corresponding mono-basic acids.[4] The two preparations gave patterns that were very similar in appearance, with different R_F values. The main fraction corresponding to dehydrovitamin B_{12} lacking the nucleotide had an R_F value (relative to that of vitamin B_{12}) of 1·85 compared with 1·7 for Factor B. The next strongest zones had relative R_F values of 1·5 and 1·3 respectively. The products were devoid of microbiological activity whereas Factor B is even more active than vitamin B_{12} in the *E. coli* plate assay.

(ii) Dehydrovitamin B_{12} (8·6 mg.) was heated with 6N-hydrochloric acid (1 c.c.) in a sealed

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tube at 100° for 2 hr. The red solution was evaporated to dryness and the residue taken up in a few drops of N-ammonia. The solution was subjected to electrophoresis on paper at pH 10 and the product shown to be a mixture of penta- and hexa-carboxylic acids. No heptacarboxylic acid was present. A parallel hydrolysis of vitamin B_{12} under the same conditions gave a mixture of penta-, hexa-, and hepta-carboxylic acids (cf. ref. 4).

Spectrophotometric Examination of the Action of Chloramine-T on Vitamin B_{12}, Dehydrovitamin B_{12}, and the Hexabasic Carboxylic Acid.—The chloramine-T used was shown titrimetrically to be 99·6% $CH_3{\cdot}C_6H_4{\cdot}SO_2{\cdot}NClNa,3H_2O$, and the procedure of Ellis *et al.*[8] was adopted. Dehydrovitamin B_{12} (10 mg.) was dissolved in 0·001N-acetic acid (100 c.c.) and to aliquot parts (20 c.c.) of this solution were added volumes (1, 2, 3, 4 c.c.) of a solution of chloramine-T (41 mg.) in water (100 c.c.), representing respectively 1, 2, 3, and 4 mols. of halogenating agent: each solution was made up to 25 c.c. with water, and, after 3 hr., examined spectrophotometrically between 500 and 600 mμ. The observations of Ellis *et al.*[8] on vitamin B_{12} were confirmed; however, in the case of dehydrovitamin B_{12} the first mol. of halogenating agent produded a bathochromic shift whereas with the hexacarboxylic acid accompanying destruction of the chromophore was rapid.

Action of Halogenating Agents on Vitamin B_{12}.—(i) (with Dr. G. W. Miller) *Chloramine-T (1 mol.).* Vitamin B_{12} (100 mg.; air-dried crystals) was dissolved in hot water (15 c.c.; ammonia-free) and to the cooled solution were added chloramine-T (22 mg.) in water (10 c.c.) and then 0·1N-hydrochloric acid (1 c.c.). No obvious colour change occurred. After 2 hr. the solution was extracted with phenol (2 × 20 c.c.), and the aqueous layer set aside for subsequent determination of ammonia. The phenol extract was washed with a little water and diluted with ether, and the red product re-extracted into a small volume of water. This solution was freeze-dried and the residue (92·5 mg.) purified by preparative electrophoresis [16] in 0·1M-potassium cyanide solution on Whatman seed-testing paper (25 × 46 cm.) at 3 v/cm. for 10 hr. Two fractions were obtained, the minor corresponding to vitamin B_{12} and referred to as the neutral fraction (although in cyanide solution it travels as a singly charged anion) and the other, the major fraction, corresponding to a monocarboxylic acid of the B_{12} series (travelling as a doubly charged anion). This main band was excised, extracted into water (Waring blendor), and freed from inorganic and insoluble material by phenol–ether extraction. Re-extraction into water, followed by freeze-drying of the solution, yielded the product (71 mg.).

This was dissolved in 1 : 1 aqueous acetone (15 c.c.), a few drops of ether were added, and the solution was kept at 0° for several days. Large crystals of the *lactone* (23 mg.) were thus obtained (Found: C, 53·0; H, 6·9; N, 12·8%; C : N, 4·15. $C_{63}H_{85}O_{15}N_{13}PCo$ requires C, 55·9; H, 6·35; N, 13·4%; C : N, 4·17. $C_{63}H_{85}O_{15}N_{13}PCo,4H_2O$ requires C, 53·0; H, 6·5; N, 12·8%). Light absorption max.: (i) in H_2O, 552, 524—525, 407—409, 359—360, 320, 302—306, and 278—279 mμ (log ε 3·88, 3·87, 3·52, 4·41, 3·88, 3·92, and 4·14 respectively); (ii) in 0·1M-KCN, 584—586, 544—545, 418—420, 368—369, 314, 306—307, 288, and 278—279 mμ (log ε 3·94, 3·87, 3·32, 4·42, 3·93, 3·91, 4·01, and 4·08 respectively). The infrared spectrum showed main peaks at 2140, 1783, 1665, 1574, 1310, 1215, 1150, 1064, 1000, 905, 870, 850, and 815 $cm.^{-1}$.

On being subjected to electrophoresis at pH 6·5 in phosphate buffer this red product had zero mobility whereas it travelled as a purple doubly charged anion in 0·1M-potassium cyanide. Treatment of a small quantity (2 mg.) with 2N-hydrochloric acid (4 c.c.) at 100° for 2 hr. yielded, after electrophoresis, tetra-, penta-, hexa-, and hepta-basic acids: similar treatment with 30% sodium hydroxide solution yielded a mixture of hexa- and hepta-basic acids.

On chromatography on paper with butan-2-ol with a trace of acetic acid as solvent, the lactone had R_F 1·2 relative to vitamin B_{12}, but after treatment with alkali the R_F was 0·6, often with a faint streak of colour terminating in a weaker spot at R_F 1·2, suggesting partial reconversion into the ring form during the chromatography. The lactone showed no microbiological activity towards the *E. coli* mutant (in plate or tube assays), *Ochromonas malhemensis*, or *L. leichmannii*.

The aqueous solution previously set aside for the determination of the ammonia liberated during halogenation was extracted continuously with ether for 2 hr., to remove traces of phenol, separated, and left under reduced pressure for 1 hr. at room temperature. After filtration the solution was concentrated to 5 c.c. and a solution (0·5 c.c.) of chloroplatinic acid (10 g.) in water

[16] Cannon and Gilson, *Chem. and Ind.*, 1954, 120.

(10 c.c.) added. After evaporation, the residue was extracted with absolute ethanol (5 c.c.), transferred to a weighed crucible, and after further washing with absolute ethanol (10 c.c.) dried to constant weight at 130°. In this way were obtained 12·6 mg. of ammonium chloroplatinate, equivalent to a recovery of 0·77 mol. of ammonia. Controls with chloramine-T and vitamin B_{12} gave residues of 1·2 and 0·6 mg. respectively. With chloramine-T (22 mg.) and 0·0104M-ammonium chloride (10 c.c.), ammonium chloroplatinate (16·4 mg.) was obtained, equivalent to a recovery of 71% of the ammonia present.

(ii) *Chloramine-T (3 mols.).* Vitamin B_{12} (500 mg.) was dissolved in acetate buffer solution (1 l.) at pH 4 and a solution of chloramine-T (310 mg. : 3 mols.) in water (50 c.c.) added. After 3 hr. the solution was extracted as described above and the halogenated product isolated as an amorphous solid (460 mg.). On being subjected to electrophoresis at pH 7 the material remained at the origin whereas in 0·1M-potassium cyanide it behaved as a monobasic acid (*i.e.*, it moved as a doubly charged anion). Chromatography on paper with butan-1-ol–acetic acid–2% hydrogen cyanide (4 : 1 : 5) showed a single spot having R_F 0·40. The light absorption spectrum in 0·1M-potassium cyanide showed max. at 288, 370, 572, and 612 mμ (Found, in amorphous material: Cl, 4·35, 4·0. Calc. for monochlorovitamin B_{12}: Cl, 2·6%).

(iii) *Bromine (1 mol.).* To a solution of vitamin B_{12} (30 mg.; hydrated crystals) in water (200 c.c.) were added acetic acid (0·015 c.c.) and then 0·047N-bromine water (0·9 c.c.) dropwise during 1 min. After 1 hr. at room temperature the red product was extracted through phenol, and an aqueous solution subjected to electrophoresis at pH 6·5 and then in 0·1M-potassium cyanide. The neutral product was extracted and crystallised (17 mg.) from aqueous acetone. Analysis of the product showed only a trace of bromine.

(iv) *Iodine (1 mol.) and sodium hydroxide.* Vitamin B_{12} (13 mg.; hydrated crystals) was dissolved in N-aqueous sodium hydroxide (10 c.c.). One half of the solution was mixed with its own volume of water and the other with the same volume of 0·1N-iodine in aqueous potassium iodide. Both solutions were kept in the dark at room temperature for 30 min., then extracted with phenol as described above and subjected to electrophoresis at pH 6·5. The major neutral zones were eluted and assayed with the *E. coli* mutant; that (3·7 mg.) from treatment with alkali alone had 70% of the activity of vitamin B_{12} and that (2·5 mg.) from treatment with the alkaline solution of iodine had 7% of the activity of the vitamin.

The latter experiment was repeated on 8 times the scale and the product fractionated on 3 sheets of Whatman 3MM paper in the ammoniacal butan-2-ol system. A faint red zone, presumably of unchanged starting material, appeared at the same R_F as the vitamin B_{12} marker. The principal zone of dehydrovitamin B_{12} had an R_F of 1·1 relative to vitamin B_{12}, and a third zone of the halogenation product ran still faster. Several other faint zones were not investigated further. The main zone corresponded with dehydrovitamin B_{12} in chromatographic behaviour, in electrophoretic behaviour at all pH values, and in its slight microbiological activity towards three test organisms.

The fastest zone also corresponded in its properties with those of the products from either chloramine-T or bromine, including the lactonic behaviour.

In another experiment vitamin B_{12} (120 mg.) was treated with a 0·1N-solution of iodine in 0·1N-sodium hydroxide at room temperature for 2¼ hr. The crude product was subjected to electrophoresis in potassium cyanide solution on Whatman seed-testing paper. The strongest zone travelled at the same rate as dicyanocobalamine and this was eluted and fractionated by chromatography on paper with, as solvent, butan-2-ol (1%) containing aqueous ammonia (*d* 0·88; 2 c.c., 4%), aqueous hydrogen cyanide (1 c.c.), and sufficient water to saturate the mixture. The zone was shown to consist mainly of the unchanged vitamin together with a little dehydrovitamin B_{12} (11 mg.). The weaker zone from the electrophoresis contained an additional acidic group, and was eluted and crystallised (32 mg.) from aqueous acetone. The electrophoretic and chromatographic properties of this substance were identical with those of the product obtained from vitamin B_{12} with either chloramine-T or bromine. The yield of product in this case greatly exceeded that of dehydrovitamin B_{12} in contrast to the previous experiment.

Acid Hydrolysis of the Lactone derived from Vitamin B_{12} by the Action of Bromine.—The product (5 mg.; hydrated crystals) from the action of bromine on vitamin B_{12} was dissolved in 11N-hydrochloric acid (0·2 c.c.) and kept at 65° for 5 min., then cooled, diluted, and extracted with cresol. The extract was washed with a small quantity of water (3 ×) to remove acid. The red product was precipitated by the addition of acetone and ether, and divided into two

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parts. One portion was dissolved in 0·1N-sodium hydroxide and the other in 0·1N-hydrochloric acid and after 30 min. the solutions were brought to pH 6·5 and subjected to electrophoresis in 0·05N-phosphate buffer (pH 6·5) containing cyanide. The patterns of purple zones so obtained were as follows :

	Acid-treated	Alkali-treated
Neutral	Strong	—
Monobasic acid	Moderate	Strong
Dibasic acid	Faint	Moderate
Tribasic acid	—	Faint

Treatment of the Monocarboxylic Acids derived from Vitamin B_{12} with Bromine.—The monobasic acids (6 mg.; hydrated crystals; mixed isomers from treatment of vitamin B_{12} with cold dilute mineral acids) were dissolved in water (20 c.c.), and acetic acid (0·003 c.c.) and 0·082N-bromine water (0·18 c.c.) were added. After 45 min. at room temperature, the mixture was acidified, extracted with cresol, and subjected to electrophoresis at pH 6·5 as described in the previous experiment. The principal product showed the same mobility as the original monocarboxylic acid. This zone was eluted and portions made acid and alkaline (to 0·05N) with hydrochloric acid and sodium hydroxide solution, each kept for 15 min., then neutralised to pH 6·5 and subjected to electrophoresis. The acidified portion still behaved as a monobasic acid but the portion treated with alkali now displayed an extra acidic group.

The experiment was repeated, with similar results, with each of the two more abundant monocarboxylic acid isomers separated by chromatography on paper.[4]

Isolation of a Crystalline Chlorinated Derivative of Dehydrovitamin B_{12}.—Dehydrovitamin B_{12} (150 mg. : air-dried crystals) was dissolved in an acetate buffer solution (1 l.) at pH 4, and a solution of chloramine-T (63 mg.; 2 mols.) in water (50 c.c.) added. After 3 hr. at room temperature the solution was extracted through phenol and ether as for the vitamin (above), and the resultant aqueous solution was washed with ether, filtered, and evaporated to small bulk under reduced pressure at 50°. Acetone was added to opalescence (total vol., 5 c.c.) and the solution left at 0°, the *product* crystallising as delicate crimson needles (46 mg.). The infrared spectrum showed that the cyanide ion was no longer present, presumably having been replaced by an hydroxo-ligand (Found : C, 53·7; H, 6·0; N, 13·4; Cl, 2·8, 3·0. $C_{62}H_{88}O_{15}N_{13}ClPCo$ requires C, 54·0; H, 6·2; N, 13·2; Cl, 2·6%). Light absorption max. : (i) in H_2O, 580, 548, 417, 365, 288, 282 mμ (log ε 3·85, 3·82, 3·43, 4·44, 4·09, 4·07 respectively); (ii) in 0·1M-KCN, 609, 568, 424, 369, 316, 303, 289 mμ (log ε 3·93, 3·82, 3·87, 3·18, 4·45, 3·82, 4·06 respectively). The infrared spectrum, determined in a potassium bromide plate, showed maxima at 3200, 2930, 1670, 1550, 1480, 1415, 1387, 1335, 1220, 1145, 1048, and 1023 $cm.^{-1}$. On subjection to electrophoresis in 0·1M-potassium cyanide the product ran as a single spot alongside vitamin B_{12} : at pH 7 it remained at the origin.

Chromatography on paper with butan-1-ol–acetic acid–2% hydrogen cyanide (4 : 1 : 5) gave R_F 0·33. The same product was obtained by using two and using five mols. of chloramine-T. With chloramine-T (1 mol.), dehydrovitamin B_{12} (150 mg.) gave the crystalline chloro-derivative (35 mg.) (Found : Cl, 2·5%), identified electrophoretically and spectrophotometrically with the product obtained previously.

Attempted Dehydrogenation of the Chromophoric System in the Hexacarboxylic Acid.—The hexabasic carboxylic acid (100 mg.) from the alkaline hydrolysis of vitamin B_{12} (preceding paper) was heated in methanol (25 c.c.) containing 11N-hydrochloric acid (1 c.c.) under reflux for 20 hr. before being evaporated to dryness under reduced pressure. The red solid (106 mg.) so obtained was extracted from a Soxhlet thimble with anhydrous benzene for 1 hr. and the extract evaporated, to yield the hexamethyl ester (43 mg.) of the acid. Light absorption max. : (i) in C_6H_6, at 345, 368, 412, 432, 525, and 555 mμ; (ii) in benzene–methanol (2 : 1) in the presence of solid potassium cyanide, 315, 367, 417, 545, and 585 mμ. At pH 7 the ester behaved as an electrophoretically neutral entity containing a trace of a monobasic acid.

Solutions of the hexamethyl ester (10 mg.) in anhydrous benzene (100 c.c.) and of chloranil (recrystallised; 11·5 mg.) in the same solvent (100 c.c.) were prepared and to aliquot samples (10 c.c.) of the ester solution were added various amounts (2 c.c., 1 mol.; 4 c.c., 2 mols.) of the chloranil solution. Heating the mixed solutions in sealed tubes at 100° for 24 hr. caused no change in colour, and spectroscopic examination confirmed that no change had taken place. More vigorous conditions (150°; 48 hr.) had no effect save to broaden the absorption peaks slightly.

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Reaction of Vitamin B_{12} with Silver Oxide.—Vitamin B_{12} (60 mg.), silver oxide (300 mg.), pyridine (3 c.c.), and ethanol (3 c.c.) were heated together under reflux for 7 min. The suspension was centrifuged and the supernatant liquid treated with ether (12 c.c.). The red precipitate was collected at the centrifuge, washed with ether, and dried. It was dissolved in water (0·5 c.c.) and streaked across four sheets of Whatman 3MM filter paper. After chromatography in the acidic butan-2-ol system (above), the main zone had R_F 1·25 (relative to that of vitamin B_{12}). There were also a weak slow zone, a fast purple zone (not further examined), and a moderately strong zone with the same R_F as vitamin B_{12}. The last zone was eluted, the solvent removed, and the residue crystallised from aqueous acetone and chromatographed again in the ammoniacal butan-2-ol system. There was then no colour at the level of the vitamin B_{12} marker spot, but all the colour was concentrated at the level of the dehydrovitamin B_{12} marker spot, with R_F 1·15 relative to that of vitamin B_{12}. This behaviour in the two solvent systems, and its neutrality on electrophoresis at pH 6·5, characterise this product as the lactam, dehydrovitamin B_{12}.

The major zone from the electrophoresis in the acidic solvent was also eluted and the solvent removed; the residue crystallised slowly from aqueous acetone. This product behaved in the same manner as the lactone (from vitamin B_{12} treated with one mol. of bromine) on chromatography and electrophoresis at pH 6·5, both in the lactone form and in the acid form (following brief treatment with aqueous alkali). The infrared spectrum also showed bands in the same positions, including the prominent band at 1785 cm.$^{-1}$ characteristic of γ-lactones.

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228. *Chemistry of the Vitamin B_{12} Group. Part VI.* The Isomeric 5 : 6-Dimethylbenziminazole Nucleotides produced by Hydrolysis of Vitamin B_{12}.*

By R. Bonnett, J. G. Buchanan, A. W. Johnson, and Sir Alexander Todd.

Hydrolysis of vitamin B_{12} under acid or alkaline conditions gives a mixture of the 2′- and the 3′-phosphate of 5 : 6-dimethyl-1-α-D-ribofuranosylbenziminazole. These have been separated by ion-exchange chromatography and their properties are recorded. The formation of these isomeric phosphates involves intermediate formation of a cyclic 2′ : 3′-phosphate as in the case of the pyrimidine and purine ribonucleotides.

The isolation of 5 : 6-dimethyl-1-α-D-ribofuranosylbenziminazole phosphate from vitamin B_{12} was first reported by Buchanan, Johnson, Mills, and Todd [1] who obtained it as an amorphous barium salt. The crystalline free acid was later obtained from an acid hydrolysate of the vitamin by Kaczka, Heyl, Jones, and Folkers [2] and again by Armitage, Cannon, Johnson, Parker, Smith, Stafford, and Todd.[3] In the meantime Brown and Todd,[4] in a discussion of the course of hydrolysis of ribonucleic acids, had shown that on treatment with acid, the individual pyrimidine or purine 2′- or 3′-ribonucleotides (the *a* and *b* nucleotides) readily formed an equilibrium mixture of the 2′- and the 3′-isomers, and that hydrolysis of their monoesters similarly yielded an equilibrium mixture, the cyclic 2′ : 3′-phosphates being intermediates in the reactions. There were no obvious

* Part V, preceding paper.

[1] Buchanan, Johnson, Mills, and Todd, *Chem. and Ind.*, 1950, 426; *J.*, 1950, 2845.
[2] Kaczka, Heyl, Jones, and Folkers, *J. Amer. Chem. Soc.*, 1952, **74**, 5549.
[3] Armitage, Cannon, Johnson, Parker, Lester Smith, Stafford, and Todd, *J.*, 1953, 3849.

reasons why the benziminazole derivatives should not behave in a similar manner and it was therefore assumed by us that the crude phosphate obtained from the acid hydrolysis of the vitamin was a mixture of the two isomers and that the position of the phosphate in the crystalline degradation product (presumably one of the two isomers) was not necessarily the same as in the parent vitamin. Paper-chromatographic evidence for the existence of two isomeric phosphates was indeed obtained and it was reported [5] that each could be converted into a cyclic phosphate hydrolysable to a mixture of the two isomers. In view of their structural analogy to the natural ribonucleotides it has become common practice to refer to these phosphates as 5 : 6-dimethylbenziminazole nucleotides or even more briefly as benziminazole nucleotides.

In a later paper [6] Kaczka and Folkers claimed that only one isomer of the benziminazole nucleotide could be detected in the products obtained from vitamin B_{12} after

FIG. 1.

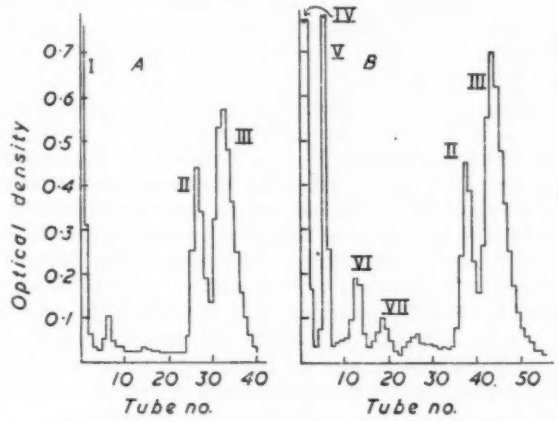

FIG. 2.

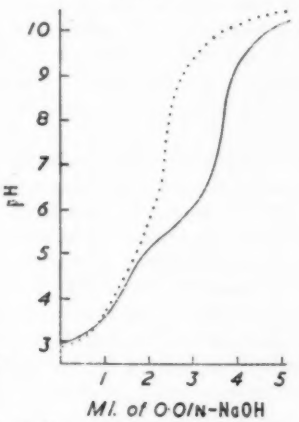

FIG. 1. *Ion-exchange separation of the 2′- and 3′-phosphate of* 5 : 6-*dimethyl*-1-α-D-*ribofuranosylbenziminazole on Dowex* 1 × 2 (*acetate*: 200—400 *mesh*: 7·5 *cm.* × 1·1 *sq. cm.*). Optical-density measurements were made at 277 mμ for the nucleotide fractions, and at 500 mμ for the coloured fractions. *A*, Separation of the isomeric nucleotides from an acid hydrolysate of vitamin B_{12}, the pigment acids being already removed (cf. Part IV); elution with water (40 c.c.), followed by 0·1N-acetic acid at a flow rate of 7 c.c./hr. *B*, Separation of the components of a previously unfractionated acid hydrolysate of vitamin B_{12}; elution with water (40 c.c.), 0·05N-acetic acid (200 c.c.) (both at 33 c.c./hr.), followed by 0·1N-acetic acid at 7 c.c./hr.

I, 5 : 6-Dimethyl-1-α-D-ribofuranosylbenziminazole; II and III, 2′- and 3′-phosphate of 5 : 6-dimethyl-1-α-D-ribofuranosylbenziminazole respectively; IV, unchanged vitamin B_{12} + Factor B; V, monobasic acid; VI and VII, dibasic acids.

FIG. 2. *Electrometric titration of the* 2′ : 3′-*cyclic phosphate of* 5 : 6-*dimethyl*-1-α-D-*ribofuranosylbenziminazole* (*broken line*). *After overnight treatment with* 4N-*hydrochloric acid, the secondary phosphoryl dissociation appears* (*full line*).

hydrolysis with 6N-hydrochloric acid at room temperature for 5—16 hr. However, treatment of the previously isolated crystalline phosphate with 80% acetic acid under reflux gave approximately equal quantities of the two isomers. They assumed therefore that the position of the phosphate group was the same in the product obtained from the hydrochloric acid hydrolyses, in the crystalline nucleotide, and in vitamin B_{12} itself. On the basis of the relative R_F values of the two isomers of the nucleotide obtained from the acetic acid isomerisation and by analogy with the properties of the *a* and *b* ribonucleotides,

[4] Brown and Todd, *J.*, 1952, 52.
[5] Todd and Johnson, *Rev. Pure Appl. Chem.*, 1952, **2**, 23.
[6] Kaczka and Folkers, *J. Amer. Chem. Soc.*, 1953, **75**, 6317.

it was suggested that the phosphate in the crystalline nucleotide and therefore in vitamin B_{12} itself was attached to the 3′-position in the sugar.

These results were clearly at variance with our own and we set out to isolate both isomers of the nucleotide in order to determine their properties and in particular their behaviour towards acid and alkali. By using a column of Dowex 1 × 2 acetate and eluting it with 0·1N-acetic acid we have shown that a mixture of the isomeric nucleotides can be resolved. Moreover, both isomers were obtained from the hydrolysis product of vitamin B_{12} with 6N-hydrochloric acid at room temperature for 18 hr. (Fig. 1). It is possible that Kaczka and Folkers's failure to detect both isomers by chromatography on paper was caused by the *a* isomer's being obscured by the coloured products of the reaction, a difficulty which does not arise with the Dowex 1 × 2 column.

Quantities of the individual nucleotides sufficient for analysis and chemical characterisation were obtained by separation of the nucleotide mixture formed [7] by alkaline hydrolysis of vitamin B_{12}. Dowex 1 × 2 was used in the chloride form in this case and the two isomers were purified by recrystallisation. As expected, each of the nucleotides was unaffected by saturated aqueous barium hydroxide at room temperature overnight, but each was isomerised to an equilibrium mixture by 6N-hydrochloric acid at room temperature overnight. The 2′ : 3′-cyclic nucleotide was obtained as an amorphous powder from either isomer by treatment with di*cyclo*hexylcarbodi-imide,[8] and treatment of it with either acid or alkali as above gave the equilibrium mixture of 2′- and 3′-nucleotides. The properties of the benziminazole 2′- and 3′-nucleotide thus parallel those of the corresponding nucleotides of the purine and pyrimidine series, apart from the variation in the ease of hydrolysis of the glycosylamine linkage, and the hydrolysis of vitamin B_{12} which yields them is strictly analogous to that of the esters of the 2′- and 3′-ribonucleotides. The position of the phosphate group in the benziminazole nucleotide of vitamin B_{12} was finally established as 3′ by *X*-ray crystallography.[9] As to which of the isolated benziminazole nucleotides is the 2′- and which the 3′-phosphate the evidence of Kaczka and Folkers [6] is, we believe, adequate to warrant the conclusion that the nucleotide isolated by them is the 3′-phosphate, and we have therefore described our materials accordingly as the 2′- and 3′-phosphate in the experimental portion of this paper.

Experimental

Chromatography of the Isomeric Nucleotides on Paper.—This was carried out with Whatman No. 1 paper in ascending chromatograms, and both layers of a mixture of 10% aqueous sodium carbonate and *iso*pentyl alcohol (1 : 1) as solvent.

Chromatograms were developed overnight, then sprayed with 20% acetic acid, and, while still moist, examined for fluorescent zones in ultraviolet light. 5 : 6-Dimethyl-1-α-D-ribofuranosylbenziminazole (the parent nucleoside) had R_F 0·27, the 2′-nucleotide R_F 0·68, and the 3′-nucleotide R_F 0·60 in this system. Aqueous sodium carbonate was found preferable to aqueous ammonium sulphate or disodium hydrogen phosphate in that better resolutions were obtained, and moreover qualitative tests for phosphate could be carried out on the paper. The above method was used throughout this work.

Separation of Nucleotides from an Acid Hydrolysate of Vitamin B_{12}.—Vitamin B_{12} (10 mg.) was treated with 6N-hydrochloric acid (2 c.c.) at room temperature for 18 hr. The product was evaporated to dryness under reduced pressure, the residue taken up in water (5 c.c.) and again taken to dryness, and the process repeated in order to remove the last traces of hydrochloric acid. The residue was adjusted to pH 9 by adding dilute aqueous ammonia, and the solution applied to a column (7·5 cm. × 1·1 sq. cm.) of Dowex 1 × 2 acetate (200—400 mesh). The column was first eluted with water (40 c.c.) which removed a mixture of unchanged vitamin

[7] Part IV, Bonnett, Cannon, Johnson, and Todd, *J.*, 1957, 1148.
[8] Dekker and Khorana, *J. Amer. Chem. Soc.*, 1954, **76**, 3522; Tener and Khorana, *ibid.*, 1955, **77**, 5349.
[9] Brink, Hodgkin, Lindsey, Pickworth, Robertson, and White, *Nature*, 1954, **174**, 1169.

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B_{12} and factor B (electrophoresis) and then with 0·05N-acetic acid which removed a monocarboxylic acid and two separate dicarboxylic acids. The column was then practically colourless and 0·1N-acetic acid was applied at a flow-rate of 7 c.c./hr. in order to displace the nucleotides. Fractions (10 c.c.) were taken throughout the separation and the nucleotide-containing fractions detected by their absorption at 277 mμ. Two separate peaks were obtained in tubes 13 and 19 which corresponded respectively to the 2′- and the 3′-nucleotide in the proportion 7 : 17. The identification was confirmed by paper chromatography.

Separation of Nucleotides from an Alkaline Hydrolysis of Vitamin B_{12}.—Crystalline vitamin B_{12} (13·21 g. in all) was hydrolysed in portions with 30% sodium hydroxide solution at 150° for 1 hr. as described previously and the 5 : 6-dimethylbenziminazole nucleotides were separated by phenol-extraction and chromatography on a column of Dowex 1 × 2 (chloride [7]), being obtained as ammonium salts (2·74 g.) contaminated with a little red material. Paper-chromatographic examination of the product as described above showed that the two isomers were present together with a small quantity of the nucleoside. A solution of the product in water (80 c.c.; pH 9) was applied to a column of Dowex 1 × 2 chloride) 10 cm. × 4 sq. cm.; 200—400 mesh) and eluted with water which removed some coloured material together with the nucleoside (68 mg.). The eluting solvent was then changed to 0·05N-acetic acid and the first 200 c.c. of eluate were examined separately. This eluate contained the remainder of the pigmented material together with nucleotide and was purified by extraction into phenol, dilution with ether, and re-extraction into water. The resulting aqueous solution was freeze-dried and the product (0·379 g.) shown by paper chromatography to consist wholly of a mixture of the isomeric nucleotides. It was dissolved in the minimum of hot water, and acetone was added until the solution just remained clear at room temperature. When the solution was kept at 0°, the pure 2′-isomer (0·214 g.) crystallised, leaving a mixture of both isomers in the red mother-liquors. The *a* nucleotide, 5 : 6-*dimethyl*-1-α-D-*ribofuranosylbenziminazole* 2′-*phosphate* was separated; it recrystallised from aqueous acetone as small colourless needles, m. p. 226—228° (decomp.) (Found: C, 46·6; H, 5·6; N, 7·7; P, 8·5, 9·0. $C_{14}H_{19}O_7N_2P$ requires C, 46·9; H, 5·4; N, 7·8; P, 8·7%). Light absorption max.: in H_2O (*ca.* pH 2), 277 and 285 mμ (log ε 3·86 and 3·83 respectively). R_F in 10% aqueous sodium carbonate–*iso*pentyl alcohol, 0·68; in butan-1-ol–acetic acid–water (4 : 1 : 5), 0·49. The infrared spectrum, determined in Nujol and hexachlorobutadiene mulls, showed max. at 3320, 3100, 2980, 2920, 2860, 2720, 2000, 1605, 1548, 1455, 1395, 1324, 1306, 1270, 1238, 1212, 1175, 1145, 1106, 1055, 969, 957, 937, 877, 869, 854, 840, 810, 765, 707, and 699 cm.$^{-1}$.

The following litre of 0·05N-acetic acid eluate was collected and the nucleotide extracted into phenol and then again into water as above described. Evaporation of the resulting aqueous solution under reduced pressure caused the pure 3′-nucleotide (0·380 g.), 5 : 6-dimethyl-1-α-D-ribofuranosylbenziminazole 3′-phosphate, to crystallise. After cooling overnight it was separated and recrystallised from aqueous acetone as small colourless needles, m. p. 238—239° (decomp.) [lit., 240—241° (decomp.)] (Found: C, 46·8; H, 5·0; N, 7·9; P, 8·2, 8·8%). The mother-liquors from the original crystallisation were freeze-dried and yielded a mixture (1·287 g.) of the nucleotides. Light absorption of the 3′-nucleotide in water (*ca.* pH 2): max. at 277 and 285 mμ (log ε 3·90 and 3·88 respectively). R_F in 10% aqueous sodium carbonate–*iso*pentyl alcohol, 0·60; in butan-1-ol–acetic acid–water (4 : 1 : 5), 0·49. The infrared spectrum, determined in Nujol and hexachlorobutadiene mulls, showed max. at 3545, 3110, 2920, 1607, 1549, 1455, 1386, 1354, 1330, 1274, 1252, 1239, 1184, 1150, 1120, 1094, 1066, 1040, 1030, 974, 925, 885, 857, 848, 809, 793, 765, and 732 cm.$^{-1}$.

The red band remaining at the top of the ion-exchange column was eluted with M-aqueous sodium chloride, and the pigment extracted with phenol in the usual manner. Electrophoretic examination showed that it consisted mainly of a cobalt-containing tetracarboxylic acid.[7]

On a small scale it was possible to separate the isomeric nucleotides completely on a column (7·5 cm. × 1·1 sq. cm.) of Dowex 1 × 2 acetate (200—400 mesh) by using 0·1N-acetic acid as the eluant and a flow rate of 7 c.c./hr. The mixed nucleotides (5 mg.) were applied as aqueous solutions of their ammonium salts at pH 9 and independent sharp peaks were obtained (i) after 210 c.c. of eluate had been collected (2′-nucleotide, R_F in 10% aqueous sodium carbonate–*iso*pentyl alcohol, 0·60) and (ii) after 270 c.c. of eluate had been collected (3′-nucleotide, R_F as above, 0·68).

5 : 6-*Dimethyl*-1-α-D-*ribofuranosylbenziminazole* 2′ : 3′-*Phosphate* (*cf. ref.* 8).—The mixed nucleotides (23 mg.) were dissolved in 10% aqueous pyridine (3·5 c.c.) and di*cyclo*hexylcarbodiimide (60 mg.) was added. The closed flask was shaken vigorously, then set aside for 2 days.

The mixture was diluted with water (5 c.c.), and the precipitated di*cyclo*hexylurea separated. The solution was extracted with ether (3 × 5 c.c.) and then lyophilised. The remaining slightly discoloured solid (19 mg.) had R_P 0·48 in the 10% aqueous sodium carbonate–*iso*pentyl alcohol system and was the 2′ : 3′-cyclic phosphate. On electrometric titration from pH 3 with 0·01N-aqueous sodium hydroxide (Fig. 2), unlike the 2′- and 3′-phosphate it did not show the secondary phosphoryl dissociation, but after treatment with cold 4N-hydrochloric acid it was reconverted into the mixed nucleotides.

Action of Acid and Alkali on the Individual Nucleotides.—(a) *Action of acid.* The nucleotide (2—3 mg.) was dissolved in 6N-hydrochloric acid and kept overnight at room temperature. Hydrochloric acid was removed under reduced pressure and the product examined by paper chromatography.

(b) *Action of alkali.* The nucleotide (2—3 mg.) was dissolved in saturated barium hydroxide solution and kept overnight at room temperature. Excess of solid ammonium carbonate was added to the product, the mixture filtered, and the filtrate examined by paper chromatography as before.

Under these conditions, the individual nucleotides were unaffected by alkali but isomerised to the equilibrium mixture by acid. The cyclic phosphate was converted into the mixed nucleotides by either acid or alkali.

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229. *An Attempted Synthesis of Perhydro-2 : 8-methylenepyridocoline.*

By K. F. JENNINGS.

Attempts to prepare the compound named in the title, from 5-nitro*iso*-phthalaldehyde, failed.

THE non-indole part of the 1954 formula for ajmaline [1] contained the cyclic system, perhydro-2 : 8-methylenepyridocoline (1-aza*tricyclo*[4 : 4 : $1^{4:8}$]undecane) (I), which has not yet been prepared. Some routes for its realisation have been examined, but without success.

A possible route appeared to be from 5-nitro*iso*phthalaldehyde to 1 : 3-di(carboxymethyl)-5-nitrobenzene and then cyclisation and reduction. *iso*Phthalaldehyde was prepared by the Sommelet reaction in good yield from *m*-xylylene dibromide and in poor yield from *m*-xylylenebishexaminium dibromide. It afforded 5-nitro*iso*phthalaldehyde in 67% yield. The Rosenmund reaction gave a tar, and the McFayden–Stevens and the Grundmann reaction gave polymers.

(I)

Attempts were then made to secure 1 : 3-di(carboxymethyl)-5-nitrobenzene from 5-nitro*iso*phthalaldehyde; the Erlenmeyer azlactone synthesis gave 5-nitro*iso*phthalylidenebis-(2-phenyloxazolone) and thence only 5-nitrophenylene-1 : 3-bis-ββ′-(α-benzamidoacrylic acid)—the methyl analogue yielded an uncrystallisable oil; the oxadiazine route [2] gave polymers at an early stage; and the rhodanine route gave a tar. Treatment of 5-nitro*iso*phthaloyl dichloride under the usual Arndt–Eistert conditions also gave a tar.

A different approach was an adaptation of Cronyn's path [3] to morphan, but 5-nitrophenylene-1 : 3-bis(ethyl benzoyloxyacetate) was obtained in very low overall yield, and the route was abandoned.

[1] Anet, Chakravarti, Robinson, and Schlittler, *J.*, 1954, 1242.
[2] Jennings, *J.*, 1957, in the press.
[3] Cronyn, *J. Org. Chem.*, 1949, **14**, 1013.

Experimental

M. p.s are corrected.

iso*Phthalaldehyde*.—Hexamine (112 g.), *m*-xylylene dibromide [4] (53 g.), and 50% acetic acid (400 ml.) were refluxed together for 2 hr., becoming homogeneous after 10 min. Concentrated hydrochloric acid (200 ml.) was added, and refluxing was continued for 10 min. When cool, the solution was poured into excess of aqueous sodium carbonate; collection and drying gave crude *iso*phthalaldehyde (11·4 g.), m. p. 78—81°. The aqueous medium was extracted with chloroform, and the crude product already obtained added to the extracts. These, after washing with water, drying (Na_2SO_4), concentration, and dilution with ether, gave the pure product (23·5 g., 88%), m. p. 88—90° (Johnston *et al.*[5] give m. p. 89°). *iso*Phthalaldehyde, in MeOH, has maxima at 2250, 2400, 2900, and 3300 Å (ε 14,200, 13,060, 1520, and 230 respectively).

m-*Xylylenebishexaminium Dibromide*.—*m*-Xylylene dibromide (26·4 g.) was added to a solution of hexamine (30 g.) in chloroform (330 ml.). After 6 hr. at room temperature the precipitate was filtered off and dried at room temperature, to give m-*xylylenebishexaminium dibromide* (57 g., 100%), m. p. 178—180° (decomp.) (Found : Hal, 39·6, 39·4. $C_{20}H_{32}N_8Br_2,CHCl_3$ requires Hal, 40·1%). In MeOH, it has maxima at 2080 and 2400 Å (ε 12,050 and 1610 respectively).

5-*Nitroiso*phthalaldehyde.—A mixture of ammonium sulphate (4 g.), concentrated sulphuric acid (12 g.), and nitric acid (2 g.; *d* 1·5) was cooled to −50°, and a solution of *iso*phthalaldehyde (1 g.) in concentrated sulphuric acid (12 g.) added, the whole allowed to attain room temperature during 12 hr. and kept thereat for a similar period. Pouring the mixture on ice gave a light yellow precipitate, which after being washed with water afforded 5-*nitroisophthalaldehyde* (0·9 g., 67%), m. p. 105—108°. This is pure enough for use. Recrystallisation from ether gave short fawn needles, m. p. 128—129° (Found : C, 53·8; H, 3·0. $C_8H_5O_4N$ requires C, 53·65; H, 2·8%). In EtOH, it has one maximum at 2300 Å (ε 13,000) and inflections at 2400 and 1650 Å (ε 13,060 and 1955 respectively). The *dioxime* had m. p. 207·5—208° (Found : C, 45·9; H, 3·4. $C_8H_7O_4N_3$ requires C, 45·9; H, 3·4%).

5-*Nitroisophthaloyl Dichloride*.—5-Nitro*iso*phthalic acid [6] (15 g., dried at 100°/15 mm. for 1 hr. before use) was refluxed with thionyl chloride (200 g.), until all had dissolved (about 48 hr.). The excess of thionyl chloride was removed *in vacuo*. The residual oil, on cooling, gave off-white needles of 5-*nitroisophthaloyl dichloride* (17·6 g., 100%), m. p. 67·5—68° (Found : N, 5·55. $C_8H_3O_4Cl_2N$ requires N, 5·65%).

Dimethyl 5-*Nitroisophthalate*.—To ice-cold ethereal diazomethane (from methyl-*N*-nitrosourea, 20 g.) was added 5-nitro*iso*phthalic acid (9·8 g.), in small portions, during a few minutes. Decolorisation was complete in 10 min., and the white precipitate was filtered off, to give dimethyl 5-nitro*iso*phthalate (10·4 g., 93%), m. p. 122—124°. Müller [7] reported m. p. 123°.

5-*Nitroisophthaldihydrazide*.—Dimethyl 5-nitro*iso*phthalate (6·85 g.) was refluxed in 100% hydrazine hydrate (3·7 g.) and ethanol (50 ml.) for 70 min. After cooling, filtration gave the *dihydrazide* (6·7 g., 98%), m. p. 237—239°. Recrystallisation from ethanol gave granules, m. p. 249—250° (Found : N, 29·0. $C_8H_{10}O_4N_5$ requires N, 29·3%). The *diethylidene derivative* had m. p. 243—244° (Found : C, 49·8; H, 4·7; N, 24·0. $C_{12}H_{13}O_4N_5$ requires C, 49·45; H, 4·8; N, 24·05%).

5 - *Nitro* - sym - *di* - N- *toluene*-p-*sulphonyl*iso*phthalhydrazide*.—5 - Nitro*iso*phthaldihydrazide (7·0 g.), and toluene-*p*-sulphonyl chloride (11·9 g.) in pyridine (120 ml.) were refluxed for 4 hr., filtered, and treated with water (500 ml.). An oil which separated solidified at 0° and on being washed, afforded 5-*nitro*-sym-*di*-N-*toluene*-p-*sulphonyl*iso*phthaloylhydrazide* (7·5 g., 47%), m. p. 243—243·5° (decomp.). Recrystallisation from acetone–ethanol gave fawn crystals, m. p. 248—248·5° (Found : C, 48·5; H, 3·7; N, 12·8. $C_{22}H_{21}O_8N_5S_2$ requires C, 48·3; H, 3·9; N, 12·8%). In EtOH, it has maxima at 2080 and 2180 Å (ε 18,860 and 20,100 respectively).

NN′-*Ditoluene*-p-*sulphonylhydrazine*.—100% Hydrazine hydrate (22 g.) and crushed ice (11 g.) were kept at 0° while, with vigorous stirring, toluene-*p*-sulphonyl chloride (37·6 g.) was added, in small portions, during 45 min. Stirring was continued for 1 hr., then filtration gave NN′-*ditoluene*-p-*sulphonylhydrazine* (26·4 g., 39%). Recrystallisation from acetone–water

[4] Kipping, *J.*, 1888, 26.
[5] Johnston and Williams, *J. Amer. Chem. Soc.*, 1947, **69**, 2065.
[6] Meyer and Wesche, *Ber.*, 1917, **50**, 444.
[7] Müller, *Ber.*, 1909, **42**, 433.

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gave white feathery needles, m. p. 219—220° (decomp.) (Found : C, 49·6; H, 4·8; N, 8·3; S, 18·5. $C_{14}H_{16}O_4N_2S_2$ requires C, 49·4; H, 4·7; N, 8·2; S, 18·8%). In EtOH, it has maxima at 2310, 2560, 2635, 2690, and 2745 Å (ε 32,000, 1530, 1700, 1600, and 1490 respectively). It is soluble in aqueous sodium hydroxide amd insoluble in hydrochloric acid, which proves the position of the acyl groups.

1 : 3-*Bisdiazoacetyl*-5-*nitrobenzene*.—To ice-cold ethereal diazomethane (from methyl-*N*-nitrosourea, 12 g.) was added powdered 5-nitro*iso*phthaloyl dichloride (3·0 g.), in small portions, in 1 min. Immediate effervescence occurred, and the product was precipitated. After a few minutes 1 : 3-bisdiazoacetyl-5-nitrobenzene (2·4 g., 77%) was filtered off, washed with ether, and dried, and thus had m. p. 143—145°. It could not be satisfactorily analysed.

3 : 5-*Bisacetoxyacetylnitrobenzene*.—The bisdiazoacetylnitrobenzene (6·4 g.) was heated in acetic acid (125 ml.) in a boiling-water bath for 2 hr. On cooling, the entire product crystallised. After being washed with water and dried, 1 : 3-*bisacetoxyacetyl*-5-*nitrobenzene* (5·4 g., 68%) had m. p. 176—177°. Recrystallisation from methanol yielded white needles, m. p. 178—179° (Found : C, 51·8; H, 4·1; N, 4·55. $C_{14}H_{13}O_8N$ requires C, 52·0; H, 4·05; N, 4·3%). In EtOH, it has one maximum at 2290 Å (ε 13,700).

*5-Nitroiso**phthalylidenebis*-(*2-methyloxazolone*).—A mixture of 5-nitro*iso*phthalaldehyde (1·8 g.), aceturic acid (2·2 g.), fused sodium acetate (1·65 g.), and acetic anhydride (5·5 g.) was heated in a boiling-water bath for 4 hr., with occasional shaking. Water (10 ml.) was added, to the cooled solution, and the dark yellow cake filtered off and washed with hot water and hot ethanol, to give the *bisoxazolone* (3·17 g., 93%), m. p. >350°; this is insoluble in the usual solvents. Before analysis, it was washed with ethanol and ether (Found : C, 55·9; H, 3·25; N, 12·0. $C_{16}H_{11}O_6N_3$ requires C, 56·3; H, 3·25; N, 12·3%). It has, in MeOH, one maximum at 2900 Å (ε 5020).

*5-Nitroiso**phthalylidenebis*-(*2-phenyloxazolone*).—5-Nitro*iso*phthalaldehyde (1·8 g.), hippuric acid (3·6 g.), fused sodium acetate (1·64 g.), and acetic anhydride (5·5 g.) at 100° for ½ hr. gave *5-nitroiso**phthalylidenebis*-(*2-phenyloxazolone*) (3·57 g., 77%), m. p. 269—271° (Found : C, 67·1; H, 3·2; N, 9·0. $C_{26}H_{15}O_6N_3$ requires C, 67·1; H, 3·2; N, 9·0%). In MeOH, it has maxima at 2400, 2600, 3000, and 3500 Å (ε 1040, 1060, 690, and 860 respectively).

5-Nitrophenylene-1 : 3-*bis*-ββ′-(α-*benzamidoacrylic Acid*).—5-Nitro*iso*phthalylidenebis-(2-phenyloxazolone) (3·0 g.) was heated with 10% aqueous sodium hydroxide (30 ml.) until dissolution was complete (about 5 min.). Water (20 ml.) was then added, and the solution made acid to Congo-red with hydrochloric acid. The precipitate was filtered off, washed with water, and dried. *5-Nitrophenylene*-1 : 3-*bis*-ββ′-(α-*benzamidoacrylic acid*) (3·1 g., 100%) thus obtained had m. p. 247—248° (Found : C, 61·6; H, 4·1; N, 8·0. $C_{26}H_{19}O_8N_3,\frac{1}{2}H_2O$ requires C, 61·2; H, 3·9; N, 8·2%). In MeOH, it has maxima at 2350, 2500, 2650, 2750, 2850, and 2950 Å (ε 45,100, 37,500, 38,500, 38,000, 34,560, and 33,250 respectively).

*5-Nitroiso**phthaloylidenebisrhodanine*.—5-Nitro*iso*phthalaldehyde (1·8 g.), rhodanine (2·66 g.), fused sodium acetate (4·92 g.), and glacial acetic acid (12 g.) were heated together at 100° for 15 min. The mixture soon became homogeneous, and then deposited the orange product. Water (25 ml.) was added to the cooled mixture, and the solid filtered off, washed, and dried to give the *bisrhodanine* (3·5 g., 85%), m. p. >300°. Recrystallisation from acetone gave yellow needles (Found : C, 41·5; H, 2·15; N, 10·1. $C_{14}H_7O_4N_3S_4$ requires C, 41·1; H, 1·7; N, 10·2%). In $CHCl_3$, it has maxima at 2650, 3000, 3650, and 3900 Å (ε 8400, 7500, 26,000, and 26,000 respectively).

m-*Nitrobenzylidenerhodanine*.—*m*-Nitrobenzaldehyde (15·1 g.), rhodanine (13·3 g.), fused sodium acetate (24·6 g.), and acetic acid (60 ml.), as above, gave m-*nitrobenzylidenerhodanine* (20·0 g., 80%), yellow needles, m. p. 270·5—271° (Found : N, 10·6. $C_{10}H_6O_3N_2S_2$ requires N, 10·5%).

5-Nitrophenylene-1 : 3-*bis*(*benzoyloxyacetonitrile*).—5-Nitro*iso*phthalaldehyde (1·8 g.) and benzoyl chloride (3·2 g.) were mixed together, and potassium cyanide (1·3 g.) in water (4 ml.) was added. The mixture became slightly brown and very hot. After 1 hr., hot water (10 ml.) was added, and, when cool, the whole was extracted with ether and then with chloroform. The two organic layers were combined and washed with aqueous sodium hydrogen carbonate (to remove benzoic acid), and then with water. After drying (Na_2SO_4), the solvents were removed, and the resultant yellow oil was treated with aqueous-ethanolic sodium hydrogen sulphite [a] (22 + 18 ml.) to remove unchanged dialdehyde. The remaining oil was washed with water and

[a] Vogel, " Practical Organic Chemistry," Longmans, London, 1948, p. 330.

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dried by distillation with methanol and benzene. In 3 weeks at room temperature, it changed to pink plates of crude 5-nitrophenylene-1 : 3-bis(benzoyloxyacetonitrile) (2·25 g., 51%), m. p. 51·5—55·5°. The infrared spectrum of this preparation was almost identical with that of pure *O*-benzoyl-*m*-nitromandelonitrile.[9] This sample could not be purified.

5-Nitrophenylene-1 : 3-bis(ethyl benzoyloxyacetate).—Crude 5-nitrophenylene-1 : 3-bis(benzoyloxyacetonitrile) (1·65 g.) was refluxed with hydrogen chloride (0·9 g.) in absolute ethanol (5·4 ml.) for ½ hr. The precipitate was filtered off, and removal of the solvent gave an oil, which on addition of ether afforded *5-nitrophenylene-1 : 3-bis(ethyl benzoyloxyacetate)* (0·15 g., 7·5%) as granular crystals, m. p. 146—150°. Recrystallisation from methanol–water gave material of m. p. 156—157·5° (Found : C, 62·4; H, 5·0; N, 2·7. $C_{28}H_{25}O_{10}N$ requires C, 62·8; H, 4·7; N, 2·6%). In EtOH, it has one maximum at 2300 Å (ε 17,300).

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[9] Ref. 4, p. 1017.

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230. *Studies in the Synthesis of Cortisone. Part XIX.* Paper Chromatography of Some Steroidal* 11 : 12-*Diols and* -*Ketols.*

By S. G. BROOKS, J. S. HUNT, A. G. LONG, and B. MOONEY.

Derivatives of tigogenin, tigogenin acetate, and tigogenone with oxygen-containing substituents at the 11-position have been made. Paper chromatography of these and of sapogenins with substituents at the 12-position and analysis of the results yield increments [ΔR_M, where $R_M = \log_{10}(1/R_F - 1)$] characteristic of each discrete polar group. The order of ΔR_M values matches the relative chemical properties of the groups. Interaction between adjacent polar groups reduces their activity, and paper chromatography shows that such influences, being subject to the familiar steric hindrances, intervene most markedly in reducing the polarity of equatorial hydroxyl groups. Consequently the simple premises of conformational analysis must be qualified for application to such compounds.

Attention to the methods of chromatography, including the use of solvents containing boric acid and exploitation of a reversible system, extend the scope of these studies.

IN earlier Parts [1] of this series we successfully used paper chromatography for analysing mixtures and testing the homogeneity of sapogenins. We attempt now to appraise the results more critically, defining the intramolecular forces between the vicinal polar groups (in ring C in particular) and confirming thereby the structures of sapogenins containing such groups.

Besides simple sapogenins isolated from plants we needed 11- and 12-hydroxy- and -oxo-sapogenins for comparison with the triols and dihydroxy-ketones. Reduction of hecogenin (XI) provided rockogenin (X) and *epi*rockogenin (IX);[2] likewise 11-oxotigogenin (VII) (or its 3-acetate, VIIa) yielded 11α- (III) and 11β-hydroxytigogenin (V),[3] the 11β-epimer being efficiently made by reduction with lithium aluminium hydride or sodium borohydride and, by the latter means, without production of sufficient 11α-alcohol to be detectable on a paper chromatogram,[4] *i.e.*, <10%. Selective oxidation of the

* Part XVIII, *J.*, 1956, 4356.

[1] (*a*) Part XIII, Elks and Phillipps, *J.*, 1956, 4320; (*b*) Part XV, Elks, Phillipps, Walker, and Wyman, *ibid.*, p. 4330; (*c*) Part XVI, Chapman, Elks, Phillipps, and Wyman, *ibid.*, p. 4344.
[2] Hirschmann, Snoddy, Hiskey, and Wendler, *J. Amer. Chem. Soc.*, 1954, **76**, 4013.
[3] Cf. Djerassi, Rosenkranz, *et al.*, *ibid.*, 1952, **74**, 1712; 1953, **75**, 1282.
[4] Klyne, *Ann. Reports*, 1954, **51**, 222; Allen, Bernstein, and Littell, *J. Amer. Chem. Soc.*, 1954, **76**, 6117.

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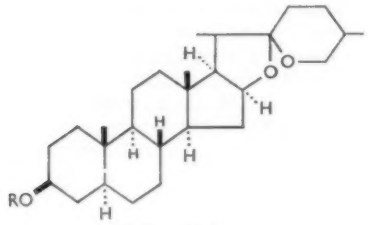
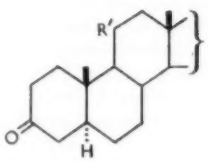
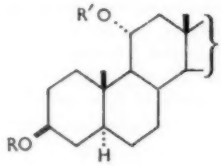
3β : 11β-diol (V) by the Oppenauer method gave 11β-hydroxytigogenone (VI), which yielded the 3 : 11-dione (VIII) when oxidised with potassium dichromate in acetone and dilute sulphuric acid.[5] This oxidant converted also the 3β : 11α- (III) and 3β : 11β-diol (V) into 11-oxotigogenone (VIII). Selective acetylation of these diols furnished the



(I) R = H †
(Ia) R = Ac



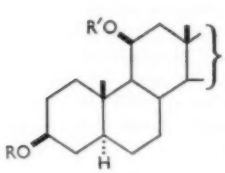
(II) R′ = H
(IV) R′ = α-OH
(IVa) R′ = α-OAc
(VI) R′ = β-OH
(VIa) R′ = β-OAc



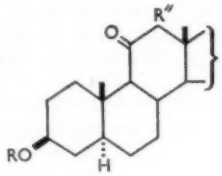
(III) R = R′ = H
(IIIa) R = Ac, R′ = H
(IIIb) R = R′ = Ac
(IIIc) R = H, R′ = Ac

† Tigogenin. The conformation of all the other compounds depicted above is that of tigogenin.

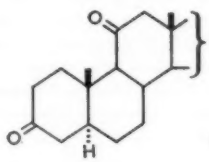
3β-acetoxy-11α- (IIIa) and -11β-alcohol (Va), the former in low yield.[6] Further acetylation of 11α-hydroxytigogenin acetate (IIIa) with acetic anhydride and pyridine gave the 3β : 11α-diacetate (IIIb), but these agents failed to esterify the 11β-hydroxy-ester (Va). We made 11β-acetoxytigogenin acetate (Vb) by using acetyl chloride and *NN*-dimethylaniline.[6b] Selective hydrolysis of the two diacetates (IIIb) and (Vb) gave the 11-acetates (IIIc) and (Vc). Final hydrolysis of the latter acetate (Vc) to the diol was tardy. Oxidation of 11β-acetoxytigogenin (Vc) with *N*-bromoacetamide in acetone gave the 11β-acetoxy-3-ketone (VIa), and acetylation of the ketol (IV) the 11α-acetoxy-ketone (IVa). We made the ketol (IV) by oxidation of the diol (III) with *N*-bromoacetamide.



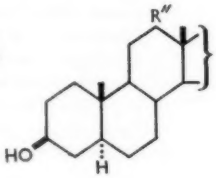
(V) R = R′ = H
(Va) R = Ac, R′ = H
(Vb) R = R′ = Ac
(Vc) R = H, R′ = Ac



(VII) R = R″ = H
(VIIa) R = Ac, R″ = H
(XII) R = H, R″ = α-OH
(XIII) R = H, R″ = β-OH



(VIII)

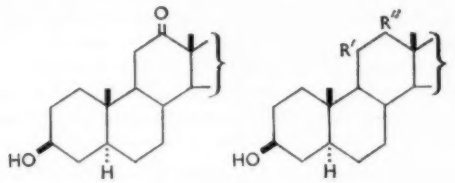


(IX) R″ = α-OH
(X) R″ = β-OH

Comparison of the properties of 11α- (III) and 11β-hydroxytigogenin (V), and, similarly of those of their esters, shows the following orders of activity: oxidation with *N*-bromoacetamide in acetone, 11β- > 3β- > 11α-; and, in contrast, oxidation with acidified aqueous potassium dichromate, 11β- > 11α- > 3β-; acetylation and hydrolysis of the ester groups, 3β- > 11α- ⩾ 11β-. Oppenauer oxidation does not affect the 11β-hydroxy-group, and oxidation catalysed by metals[4] is probably similarly selective. *N*-Bromoacetamide has already been shown to oxidise 11β-alcohols in preference to their epimers and 3α-hydroxy-5β-steroids,[7] and *tert.*-butyl hypochlorite to oxidise a 3- in preference to an

[5] Bladon, Henbest, Jones, Lovell, and Woods, *J.*, 1954, 125.
[6] (*a*) Rosenkranz, Mancera, and Sondheimer, *J. Amer. Chem. Soc.*, 1954, **76**, 2227; (*b*) Crawshaw, Henbest, and Jones, *J.*, 1954, 731.
[7] Mancera, Romo, Sondheimer, Rosenkranz, and Djerassi, *J. Org. Chem.*, 1952, **17**, 1066; Herzog, Jevnik, and Hershberg, *J. Amer. Chem. Soc.*, 1953, **75**, 269; Hanze, Fonken, McIntosh, Searcy, and Levin, *ibid.*, 1954, **76**, 3179; Jones and Kocher, *ibid.*, p. 3682; cf. refs. 3, 4, and 12.

11α- or 11β-hydroxyl group.[8] However, chromatography of the products of some of our attempts at selective conversions betrayed their shortcomings (cf. Experimental section).



(XI)

(XIV) R′ = R″ = α-OH
(XV) R′ = β-OH, R″ = α-OH
(XVI) R′ = R″ = β-OH
(XVII) R′ = α-OH, R″ = β-OH

In assessing the intramolecular bonding in our sapogenins we have used their behaviour on paper chromatograms to test the relative strengths of their polar groups. In general, simple stanols with equatorial hydroxyl groups are more polar, and consequently have lower R_F values, than the isomers with axial groups,[9] although a few exceptions reveal unexpected steric effects.[10-12] Interaction between polar groups in steroids has not been studied by its effect on the R_F values, but the paper chromatography of sugars and cyclitols [13-15] suggests that vicinal equatorial hydroxy-groups engage in the strongest intramolecular bonding.

Martin [16] has propounded an explanation of partition chromatography by means of which a function $R_M = \log_{10}(1/R_F - 1)$ can be related to the free-energy change accompanying transport of the molecule from one phase to the other. To a satisfactory approximation (the R_M values being a measure of the chemical potential of the compound), the components of the molecule contribute additively; the function may therefore be likened to the parachor [17] or to Hammett's [18] substituent constant σ. Bate-Smith and Westall [19] showed that a further hydroxyl group introduced into the *ortho*-position of a phenol contributed less to the R_M value than one entering the *meta*-position. For our purpose, therefore, we deduced the contributions due to isolated hydroxy- and keto-groups in various positions in the steroidal sapogenins, with a view to calculating subsequently the discrepancies arising when such groups are juxtaposed. An earlier attempt to formulate the behaviour of steroids on paper chromatograms was based on different premises.[20]

Using the procedures devised by Sannié and Lapin [12] and by Heftmann and Hayden [21] for the paper chromatography of steroidal sapogenins, we produced chromatograms with discrepancies in the R_F values of $\geqslant 0{\cdot}03$, and with satisfactory reproducibility in the ΔR_M values calculated for the 11α- and 11β-hydroxy- and 11- and 12-oxo-groups of derivatives of tigogenin, tigogenin acetate, and tigogenone. The consistency, and the roundness of the spots on the chromatograms, as well as the propensity of the compounds to run in the solvent front in slightly more polar solvent systems, confirm the predominance of partition

[8] Fonken, Thompson, and Levin, *J. Amer. Chem. Soc.*, 1955, **77**, 172; ref. 7.
[9] Savard, *J. Biol. Chem.*, 1953, **202**, 557; *Recent Progr. in Hormone Res.*, 1954, **9**, 185.
[10] Kochakian and Stidworthy, *J. Biol. Chem.*, 1952, **199**, 607.
[11] Axelrod, *ibid.*, 1953, **205**, 173; *Recent Progr. in Hormone Res.*, 1954, **9**, 208; cf. Dirscherl and Gerhards, *Acta Endocrinol.*, 1955, **19**, 233.
[12] Sannié and Lapin, *Bull. Soc. chim. France*, 1952, 1080.
[13] Cifonella and Smith, *Analyt. Chem.*, 1954, **26**, 1132.
[14] Kowkabany, *Adv. Carbohydrate Chem.*, 1954, **9**, 303.
[15] (*a*) Isherwood and Jermyn, *Biochem. J.*, 1951, **48**, 515; (*b*) Mulvany, Agar, Peniston, and McCarthy, *J. Amer. Chem. Soc.*, 1951, **73**, 1255; (*c*) Posternak, Raymond, and Haerdi, *Helv. Chim. Acta*, 1955, **38**, 191.
[16] Martin, *Biochem. Soc. Symposia*, 1949, No. 3, p. 4; cf. ref. 19.
[17] Brimley and Barrett, "Practical Chromatography," Chapman and Hall, Ltd., London, 1953, p. 42.
[18] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, 1940, p. 184.
[19] Bate-Smith and Westall, *Biochim. Biophys. Acta*, 1950, **4**, 427; Bradfield and Bate-Smith, *ibid.*, p. 441; Martin, *Discuss. Faraday Soc.*, 1949, **7**, 332.
[20] Grundy, Simpson, and Tait, *Nature*, 1952, **169**, 795.
[21] Heftmann and Hayden, *J. Biol. Chem.*, 1952, **197**, 47.

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effects; appreciable adsorption on to the paper (which intervenes in the paper chromatography of some steroids [22]) is undesirable, especially as elution of adsorbed steroids defies a simple explanation, presumably owing to deformations in the molecules.[23] Our evidence indicates that the effects of substituents at the 3- and the 11-position are discrete. Calculations (recorded in the Experimental section) of molecular rotations confirm this impression, although they disclose anomalies for 11α- and 11β-acetoxy-groups.

Further calculations (see Table 1) show how published data yield increments attributable to the 11β- and 17α-hydroxy- and 11-oxo-substituents in corticoids, from

TABLE 1. *Derivatives of* 21-*hydroxypregn*-4-*ene*-3 : 20-*dione* (11-*deoxycorticosterone*).

				R_M Values [a]			
Derivative	B_1	B_2 [b]	B_3	Sakal and Merrill [c,g]	Schmidt *et al.* [h]	Hofmann *et al.* [i]	Pechet [j]
11β-Hydroxy-	0·53	−0·27	0·75	−0·27	0·35	0·43	−0·75
17α-Hydroxy-	0·43	−0·37	0·60	−0·37	0·69	0·75	−0·83
11-Oxo-	0·25	−0·48	0·48	—	—	—	−0·91
Parent compound	−0·79	−1·28	−0·48	−1·06	0·95	1·00	−1·10
Group				ΔR_M Values [d]			
11β-Hydroxy-	1·31	1·01	1·23	0·79	0·61 [e]	0·57 [e]	0·34
17α-Hydroxy-	1·22	0·91	1·08	0·69	0·27 [e]	0·25 [e]	0·27
11-Oxo-	1·04	0·80	0·95	—	—	—	0·19 [e]
Comparison of calculated [f] *and observed* R_M *values.* [a]							
11β : 17α-Dihydroxy- (Cortisol)							
Calc.	1·74	0·64	1·83	0·42	0·07	0·18	−0·38
Obs.	1·51	0·95	2·00	0·25	0·04	0·25	−0·16
17α-Hydroxy-11-oxo- (Cortisone)							
Calc.	1·47	0·43	1·55	—	—	—	−0·64
Obs.	1·28	0·60	1·69	0·00	0·05	0·27	−0·41

[a] Calc. from Bush's results (for solvent systems B_1, B_2 and B_3) (*Biochem. J.*, 1952, **50**, 370) and the other sources cited. [b] The R_F values in this system were too high for accurate calculation. [c] Dried paper. The separations secured were not very sharp; undried papers gave poorer results. [d] Calc. from the four rows above in the Table. [e] Signs reversed. [f] Calc. from figures in the two sections above in the Table. [g] Sakal and Merrill, *Science*, 1953, **117**, 451. [h] Schmidt, Staudinger, and Bauer, *Biochem. Z.*, 1953, **324**, 128. [i] Hofmann and Staudinger, *ibid.*, 1951, **322**, 230. [j] Pechet, *J. Clin. Endocrinol. Metab.*, 1953, **13**, 1542.

which R_M and R_F values for cortisone and cortisol can be derived in fair agreement with those found by experiment. These results again refute the existence in the dissolved steroid of strong intramolecular hydrogen bonds implicating hydroxy- and keto-substituents at the 11-position. Although 17α-hydroxypregnan-20-ones contain bonds of this type, which are detectable by infra-red spectroscopy [24] and by anomalous optical rotations,[25] they have not been noticed in the 17α : 21-dihydroxy-20-ketone system. We shall discuss this below.

Table 1 contains results for aqueous solvent systems. Burton, Zaffaroni, and Keutmann [26] devised means of resolving mixtures of corticoids in non-aqueous solvent systems containing, for example, propylene glycol or formamide as the polar component. This practice has been widely adopted, but the R_F values of corticoids in such systems may be too low for direct measurement; therefore the results are generally given as R_T values, the R_T of a compound being proportional to the ratio of its R_F to that of a standard.[9] Provided that the R_F of the standard is small compared to unity and to $1/R_T$, $\Delta R_M = -\log_{10} R_T$ approximately, where ΔR_M is the contribution of the group distinguishing the steroids under comparison. Applying this equation to the data of

[22] Cf. Smith, *J. Amer. Chem. Soc.*, 1954, **76**, 3232.
[23] Brooks, Klyne, and Miller, *Biochem. J.*, 1953, **54**, 212.
[24] Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2820; cf. Fukushima, Dobriner, Heffler, Kritchevsky, Herling, and Roberts, *ibid.*, 1955, **77**, 6585.
[25] Norymberski, *J.*, 1954, 762; cf. Bloom, Agnello, and Laubach, *Experientia*, 1956, **12**, 27.
[26] Burton, Zaffaroni, and Keutmann, *J. Biol. Chem.*, 1951, **188**, 763.

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Burton *et al.*, we find ΔR_M values as follows for the groups mentioned in Table 3: 17α-hydroxy-, 0·85; 11β-hydroxy-, 0·69; 11-oxo-, 0·30. The aggregate ΔR_M value calculated for the substituents at the 11- and the 17-position is 1·16 in cortisone and 1·55 in cortisol, in fair agreement with the increments of 1·39 and 1·77 deduced from the data given for these compounds and 11-deoxycorticosterone. Savard's results [9] with systems composed of propylene glycol and light petroleum or toluene testify to the excellence of the resolution and afford the ΔR_M values set out in Table 2, the approximate equation being used when the implicit assumptions seemed justifiable. The weaker influence of the 17α-hydroxy-group in the 21-deoxy series reveals the hydrogen-bonding in these compounds, mentioned above, and the low polarity of the 21-hydroxyl and enhanced activity of the 17-hydroxyl in the 20-oxo-17 : 21-diols suggest that in these compounds the primary displaces the tertiary hydroxyl in the association with the keto-group.

TABLE 2. ΔR_M *Values for hydroxyl groups.*[a]

Mobile phase [b]	6α	6β	11α	11β	14α	16α	17α [c]	17α [d]	21 [c]
Light petroleum ...	1·92	1·33	1·70	1·19	1·36	1·70	0·92	1·17	0·71
	(0·05)	(0·11)	(0·15)	(0·09)	(0·18)				
Toluene	1·88	1·40	1·46	1·15 [e]	—	1·96	0·98	1·32	*ca.* 0·4
		(0·18)		(0·20)			(0·17)		

[a] Calc. from Savard's data [9] from the equation $\Delta R_M = -\log_{10} R_T$ (see text). Values in parentheses indicate limits of error, where two or more calculations could be made. [b] Stationary phase: propylene glycol. [c] In 17α : 21-dihydroxy-20-oxopregnanes. [d] In 17α-hydroxy-20-oxopregnanes. [e] 11-Oxo, $\Delta R_M = 0·79$ (0·12).

The high resolving power of the solvent systems used in our initial experiments hindered extension of these methods to dihydroxy-keto- and trihydroxy-sapogenins, because in conditions suitable for these the monohydroxy-compounds had R_F values too high to permit accurate calculation. We overcame this difficulty by reversing the roles of the phases: with the predominantly aqueous phase flowing, we achieved adequate resolving power and satisfactory R_F and R_M values (cf. refs. *h*—*j* of Table 1) and, the phases having been transposed, the more polar sapogenins outdistanced the monohydroxy-compounds. With the most suitable reversible solvent system (described in the Experimental section as D) corticoids and their 21-acetates, most of which were more polar than the sapogenins, were separated satisfactorily when the predominantly aqueous phase was used as the stationary component; ΔR_M values calculated in this way for the 11β-hydroxy- and 11-oxo-groups in these compounds were nearly equal (but of opposite sign) to the corresponding increments obtained from the R_F values of the sapogenins run with the phases reversed (see Table 3). Such agreement suggests a likely extension of the present methods satisfactorily to steroids of widely differing polarities.

We have been able to confirm the anomalous behaviour of rockogenin (X) and *epi*rockogenin (IX) in some solvent systems; [12] when they run in the expected order, *i.e.*, with the former (12β-hydroxy; equatorial) behaving as the more polar epimer, the separation is small. Most of our calculations pertain to systems in which these epimers run normally. The anomaly may be attributed to the formation of solvates that detract mostly from the polarity of the more hydrophilic groups; a similar explanation has been adduced in the course of comments on peculiarities in the paper chromatography of sugars.[15a] Or we could presume that the 12β-hydroxyl tends to form a bond with one of the oxygen atoms in the *spiro*ketal system or is hampered by groups or atoms in rings E and F (*e.g.*, at the 20-position),[27] just as the 19α(equatorial)-substituent in the triterpenoid nucleus [28] suffers interference from the hydrogen atoms at $C_{(12)}$. It is noteworthy in the present context that the rotational contribution (ΔM_D −9°) of the 12β-hydroxyl group to

[27] (*a*) Callow, Dickson, Elks, Evans, James, Long, Oughton, and Page, *J.*, 1955, 1966; (*b*) cf. Mueller, Stobaugh, and Winniford, *J. Amer. Chem. Soc.*, 1953, **75**, 4888.

[28] Ames, Beton, Bowers, Halsall, and Jones, *J.*, 1954, 1905; cf. Klyne, *Experientia*, 1956, **12**, 119; Rothman and Wall, *J. Amer. Chem. Soc.*, 1956, **78**, 1744; Hassall and Reyle, *Chem. and Ind.*, 1956, 487.

the molecular rotation of rockogenin is abnormal, whereas that (ΔM_D + 107°) of the 12α-hydroxyl in *epi*rockogenin is normal; Barton and Klyne [29] give +50° and +93° as average values for such contributions. The effects of changes in the side chain on the stability of the 12-hydroxy-11-keto-steroids have been discussed in another paper.[1c]

TABLE 3. ΔR_M [a] *Values for various groups* [b] *in steroidal sapogenins.*

	3-Oxo	3β-OH	3α-OH	11-Oxo	11α-OH	11β-OH	12-Oxo	12α-OH	12β-OH	15β-OH
Solvent DR [c]	0·83	1·09 [c]	—	0·62 [f]	1·29	0·95 [f]	0·69	1·13	1·18	0·40
	0·69 [d]	0·94 [d]	1·09 [d]	—	—	—	—	—	—	—
Solvent E ...	—	—	—	0·53	1·34	0·93	0·91	1·16	1·30	0·56

[a] The values for the substituents at the 3-position were calculated with deoxysmilagenin as the reference compound, and all the others from tigogenin (I) or tigogenone (II). [b] In the tigogenin series, unless otherwise stated; cf. previous footnote and footnotes *d* and *e*. [c] Signs of ΔR_M values reversed. [d] For 5β-series, *i.e.*, smilagenin and related compounds. [e] For the 3β-OH in diosgenin, ΔR_M = 1·19. [f] Mean ΔR_M values calc. from R_F values of cortisone, cortisol, and Reichstein's compound S and their 21-acetates, run in solvent D: 11-oxo-, 0·60; 11β-OH, 0·94.

Using the figures in Table 3, we could assess the differences (δ) between the calculated and observed R_M values for the 12-hydroxy-11-oxo- and 11 : 12-dihydroxy-tigogenins. Table 4 shows the satisfactory agreement between the conclusions reached when a solvent system was used ordinarily or (probably with slightly greater accuracy) with the usual functions of the phases reversed. The conclusions testify to bonding in the 12β-hydroxy-11-ketone (XIII) stronger than in its epimer (XII); indeed, so marked is the difference that the latter behaves as the more polar form, in spite of the slightly greater polarity of the hydroxyl group in rockogenin (X) compared with that in *epi*rockogenin (IX). The ketolic glycosides leptoside and inertoside (in another solvent system) are not so anomalous, for the latter (with a 12α-hydroxy-group) outruns its epimer; [30] however, the isomeric 11α-hydroxy-12-ketone intermedioside runs further than both, intramolecular bonding

TABLE 4. *Detection of intramolecular bonding (by δ values).*

	Solvent system DR [a] R_M Values			Solvent system E R_M Values		
Tigogenin deriv.	Calc.[b]	Found	δ [c]	Calc.[c]	Found	δ [c]
12α-Hydroxy-11-oxo-	1·15	0·75	0·40	0·57	0·37	0·20
12β-Hydroxy-11-oxo-	1·20	0·39	0·81	0·71	−0·14	0·85
11α : 12α-Dihydroxy-	1·82	0·83	0·99	1·38	0·69	0·69
11β : 12α-Dihydroxy-	1·48	0·95	0·53	0·97	1·12	−0·15
11β : 12β-Dihydroxy-	1·53	0·72	0·81	1·11	0·53	0·58
11α : 12β-Dihydroxy-	1·87	0·87	1·00	1·52	0·79	0·73

[a] Signs of R_M and δ values reversed. [b] From the increments given in Table 3. [c] For meaning, see text.

obviously outweighing the superiority in polarity that the unaffected 12-oxo- and equatorial 11α-hydroxy-groups would otherwise bestow on it. (These last compounds are 14β-hydroxy-steroids with rings C and D *cis*; the steric effects would therefore differ in detail from those considered for the sapogenins.) Anomalies in the rates of oxidation of 11-hydroxy-12-oxo-steroids have also been observed.[31]

The figures in Table 4 also reveal appreciable vicinal effects in the diastereoisomeric 11 : 12-dihydroxytigogenins. Although the order of running defies any simple explanation, the δ values are rational, the most marked interplay occurring between the two equatorial hydroxy-groups and between the 11α(equatorial)- and 12α(axial)-groups. The doubly axial 11β : 12α-diol system is least affected by intramolecular forces. The axial 12α-hydroxyl group allows strong bonding in the 11α : 12α-dihydroxy-system, but the 11β-hydroxy-group in 11β : 12α- and 11β : 12β-dihydroxy-tigogenin is evidently reluctant to be so engaged.

[29] Barton and Klyne, *Chem. and Ind.*, 1948, 755.
[30] Hegedüs, Tamm, and Reichstein, *Helv. Chim. Acta*, 1955, **38**, 98; Schindler, *ibid.*, 1956, **39**, 64.
[31] Archer, Lewis, Martini, and Jackman, *J. Amer. Chem. Soc.*, 1954, **76**, 4915.

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Addition of boric acid [32,33] to the solvents used for our paper chromatograms markedly affected the progression of derivatives containing the 11α : 12α- and 11β : 12β-diol systems. This influence is most aptly expressed as the change ($\Delta R_M{}^B$) in R_M value brought about by the addition of the acid. The figures compared in Table 5 show that the results are nearly the same when the roles of the solvents are reversed. The use of boric acid and reversal of the phases permit separation and identification of each of the four diastereoisomeric forms of 11 : 12-dihydroxy-tigogenin, the unmodified systems being of inadequate resolving power. The hydroxyl groups spanned by the acid might in this way be protected, for example, from oxidation.[34]

TABLE 5. *Effects of boric acid on the paper chromatography of the 11 : 12-dihydroxytigogenins.*

vic.-Diols (tigogenin derivatives)	R_M Values			R_M [a] Values		
	Solvent D	Solvent DB	$\Delta R_M{}^B$	Solvent DR	Solvent DBR	$\Delta R_M{}^B$
11α : 12α- (e, a)	−0·11	−0·91	0·80	0·83	0·18	0·65
11β : 12α- (a, a)	0·21	0·05	0·16	0·95	0·69	0·27
11β : 12β- (a, e)	−0·37	−0·69	0·32	0·72	0·29	0·43
11α : 12β- (e, e)	0·02	−0·04	0·06	0·87	0·66	0·21

[a] Signs of the R_M and $\Delta R_M{}^B$ values reversed; for the meaning of the latter function, see text.

EXPERIMENTAL

Unless other conditions are mentioned, the description below is of our regular practice. Measurements of optical rotation and ultraviolet absorption were on solutions of the steroids in $CHCl_3$, and of infrared absorption on CS_2 solutions. The method of measuring infrared absorption has been described elsewhere.[35] Grade O alumina (Peter Spence and Sons Ltd., Widnes, Lancs.) was used for chromatography. The products of reactions were either precipitated by water from water-miscible solvents, washed with water, and dried, or extracted into a water-immiscible solvent, washed with aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and filtered, the solvent being then distilled to dryness under reduced pressure. The structures of compounds identified with authentic specimens were confirmed by mixed m. p. and infrared spectroscopy. M. p.s were measured with a Kofler block.

All the sapogenins described herein gave in the infrared absorption characteristic of *iso*spirostans,[36] but only the positions of maxima due to carbonyl groups are mentioned.

Molecular-rotation Differences.—Acyloxy-groups at the 11-position affect the contributions at the 3-position. Thus for acetylation and oxidation (to the 3-ketone) of the 3β-hydroxyl group, the following ΔM_D values were observed: [37] (I), −54°, +60°; (VII), −41°, +77°; (III), −15°, +57°; (IIIc), +37°, +104°; (V), −54°, +46°; (Vc), −2°, +46°.

Contributions (ΔM_D) from the substituents at the 11-position for derivatives of tigogenin (I), tigogenin acetate (Ia), and tigogenone (II) are as follows. 11α-Acetoxy: (IIIc), −183°; (IIIb), −114°; (IVa), −139°. 11-Oxo: (VII), +123°; (VIIa), +136°; (VIII), +140°. 11α-Hydroxy: (III), −70°; (IIIa), −31°; (IV), −73°. 11β-Hydroxy: (V), +25°; (Va), +25°; (VI), +9°. 11β-Acetoxy: (Vc), +72°; (Vb), +60°; (VIa), +124°.

Paper Chromatography.—The solvents were run downwards in the usual type of apparatus,[27a] kept at 30° ± 0·5°; the solvents ("AnalaR" or distilled) were kept at this temperature for several hours before use. The papers (Whatman No. 2) were exposed to the vapour over the mixture for at least 40 hr. before solvent was allowed to run over them. If the mixture separated into two phases, the paper was exposed in the equilibration stage to both. In two-phased mixtures, the less aqueous layer provided the moving phase, unless the functions were reversed (such conditions being designated by the letter R after the description of the solvent;

[32] Boeseken, *Adv. Carbohydrate Chem.*, 1949, **4**, 189; Zittle, *Adv. Enzymol.*, 1951, **12**, 493; cf. Kowkabany, ref. 14.
[33] Angyal and McDonald, *J.*, 1952, 686.
[34] Cf. Zittle, ref. 32, p. 500; Staple, *Nature*, 1955, **176**, 1125; Brutcher, Roberts, Barr, and Pearson, *J. Amer. Chem. Soc.*, 1956, **78**, 1507.
[35] Dickson, Page, and Rogers, *J.*, 1955, 443.
[36] See ref. 27*a* for literature.
[37] Cf. Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, 1949, p. 208.

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the running times were then increased by about 50%). Mixtures designated by the letter B contained 8·5% (w/v) of boric acid, and the papers were dipped in 5% (w/v) aqueous boric acid and dried at room temperature before they were used.

The sapogenins were located on the chromatograms by Komarowsky's reagent,[27a] by means of which about 4 μg. were detectable; phosphomolybdic [38] and trichloroacetic acid [21] were less sensitive as reagents.

The R_F values of several selected sapogenins varied by a standard mean deviation of ±0·03 on more than a dozen chromatograms and were reproducible when the specimens were included in mixtures.

The R_F values included in Table 6 were obtained in the above fashion. Values given elsewhere in this Experimental section were obtained with solvent system F4 (see below). R_M values accurate enough for most purposes were calculated from a plot of $R_M = \log_{10}(1/R_F - 1)$; the resolving power ($\Delta R_F/\Delta R_M$) was obviously greatest when $R_F = 0{\cdot}5$. When $R_F < 0{\cdot}2$, $R_M = -\log_{10} R_F$ approx.

Solvent Systems.—In this section light petroleum means the fraction, b. p. 60—80°, and the chloroform was alcohol-free. Times for the running solvent to move about 35 cm. are given. Systems A to E were based on data in reports by Heftmann and Hayden [21] and by Bush,[39] and F to I on systems used by Sannié and Lapin [12] and by Callow *et al.*[27a]

(A) Light petroleum (400), ethanol (10), toluene (100), water (90), 95 min. (B) As (A), except toluene (50), 95 min. (C) As (A), but no toluene, 140 min. (D) Light petroleum (250), methanol (600), toluene (500), water (300), 95 min. (E) As (C), except ethanol (200), 100 min. (F) Light petroleum (500), chloroform (50), acetic acid (5), 110 min. (G) As (F), except light petroleum (250), and benzene (250), 95 min. (H) Chloroform (50), acetic acid (5), benzene (500), 120 min. (I) Light petroleum (500), acetic acid (10), 95 min. (J) Light petroleum (500), methanol (10), 105 min. (Tetrahydrofurfuryl alcohol, *NN*-dimethylformamide, 2-methoxyethanol, nitromethane, and ethyl acetate could be used without advantage instead of methanol.) (K) Light petroleum (500), pyridine (10), 105 min. System F4 was the same as F, except that it was used at room temperature, equilibrated overnight, and run on Whatman No. 4 papers; the separations were then not quite as sharp as with F.

The following compounds used in this work as starting materials had m. p.s and rotations in agreement with specimens described in the literature:[40] tigogenin (I), R_F 0·85 (sublimes readily at 170—180°/10^{-1} mm.); tigogenin acetate (Ia), R_F 0·95; hecogenin (XI), R_F 0·74; hecogenin acetate (XIa), R_F 0·89; rockogenin (X); *epi*rockogenin (IX). Spectra of Nujol mulls of tigogenin gave a peak at 1665 $cm.^{-1}$, absent from the spectra of solutions and from all the spectra of the acetate (Ia), from which it was derived or into which it was converted.

Professor D. H. R. Barton provided us with specimens of deoxysmilagenin, *epi*sarsasapogenin, smilagenin, smilagenone, digitogenin, and sarsasapogenin from the late Professor Kon's collection.[41] They appeared pure by paper chromatography. (The two last-named were also obtained from Light & Co., Poyle, Colnbrook, Bucks.) Professor Kon's two samples [42] of 3-methylsarsasapogenin, m. p. 179—180° and 188—189°, are mixtures whose properties are discussed below. His specimen of gitogenin (m. p. 273—277°) was contaminated with a more polar sapogenin (see Table 6).

Tigogenone (II).—Tigogenin (I) (10 g.) was oxidised [5] in refluxing "AnalaR" acetone (500 ml.) with a solution of 0·33M-potassium dichromate in 4N-sulphuric acid (30 ml.; 1·25 equiv.). After 5 min. the green solution was poured into water (2 l.), and the precipitate, after being washed with water and dried, crystallised from acetone as needles (7·9 g., 80%) of tigogenone (II), m. p. 204—208° (subliming at 140—170°/10^{-5} mm.), $[\alpha]_D^{29}$ −50° (*c* 0·51), −35° (*c* 0·58 in pyridine), $\nu_{max.}$ 1710 $cm.^{-1}$, R_F 0·92. Its 2 : 4-*dinitrophenylhydrazone* formed yellow needles, m. p. 260—266°, $[\alpha]_D^{25}$ −44° (*c* 0·45), $\lambda_{max.}$ 368·5 mμ (ε 29,100), on chromatography on alumina and crystallisation from ethyl acetate (Found: N, 9·55. $C_{33}H_{46}O_6N_4$ requires N, 9·4%).

[38] Kritchevsky and Kirk, *Arch. Biochem. Biophys.*, 1952, **35**, 346; cf. ref. 27*a*.
[39] Bush, *Biochem. J.*, 1952, **50**, 370.
[40] Wall, Krider, Rothman, and Eddy, *J. Biol. Chem.*, 1952, **198**, 533; Klass, Fieser, and Fieser, *J. Amer. Chem. Soc.*, 1955, **77**, 3829; cf. ref. 17.
[41] Kon, Soper, and Woolman, *J.*, 1939, 1201; Marker and Rohrmann, *J. Amer. Chem. Soc.*, 1939, **61**, 943.
[42] Bolt and Backer, *Rec. Trav. chim.*, 1937, **56**, 1139; Farmer and Kon, *J.*, 1937, 414; Kuwada and Miyasaka, *J. Pharm. Soc. Japan*, 1938, **58**, 540; Barton, *Experientia*, 1955, Suppl. II, p. 121; B.P. 738,576; U.S.P. 2,713,061.

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TABLE 6. *R_F Values in various solvent systems.*

No.	Compound	A	B	C	D	E
1	Deoxysmilagenin	1·00	1·00	1·00	1·00	0·95
2	Sarsasapogenin	0·91	0·90	0·90	0·95	0·93
3	*epi*Sarsasapogenin	0·84	0·78	0·74	0·90	0·86
4	Smilagenin	0·93	0·90	0·90	0·95	0·93
5	Tigogenin (I)	0·88	0·80	0·77	1·00	0·93
6	Diosgenin	—	0·80	0·77	1·00	0·93
7	Smilagenone	0·99	1·00	0·98	1·00	0·94
8	Tigogenone (II)	0·99	0·97	0·98	1·00	0·94
9	11-Oxotigogenone (VIII)	0·98 *	0·87	0·80 *	1·00	0·85
10	3-Methylsarsasapogenin	0·95	0·92	0·73 0·87	1·00	0·91
11	Hecogenin (XI)	0·50	0·31	0·15	0·95	0·62
12	11-Oxotigogenin (VII)	0·71	0·50	0·33	0·90	0·73
13	Rockogenin (X)	0·43 *	0·26	0·22 *	0·83	0·40
14	*epi*Rockogenin (IX)	0·30 *	0·14	0·15	0·80	0·48
Tigogenin derivatives						
15	11α-Hydroxy- (III)	0·25	0·13	0·10 *	0·78	0·38
16	11β-Hydroxy- (V)	0·50	0·36	0·22	0·90	0·61
17	12α-Hydroxy-11-oxo- (XII)	0·16 *	0·09 *	0·03 *	0·72	0·30
18	12β-Hydroxy-11-oxo- (XIII)	0·53	0·35 *	0·23	0·88	0·58
19	11α : 12α-Dihydroxy- (XIV)	0·15 *	0·10 *	0·07 *	0·56	0·17
20	11β : 12α-Dihydroxy- (XV)	0·07 *	0·04 *	0·02 *	0·38	0·07
21	11β : 12β-Dihydroxy- (XVI)	0·14 *	0·08 *	0·03 *	0·70	0·23
22	11α : 12β-Dihydroxy- (XVII)	0·13 *	0·08 *	0·05 *	0·49	0·14
23	Gitogenin	—	0·05 0·12	0·03 * 0·07	0·70 0·80	0·37 0·68
24	Digitogenin	0·07	0·04	0·03		0·37

No.	F	G	H	I	J	K	DB	DR	DBR
1	0·98	1·00	1·00	0·97	1·00	0·97	1·00	0·02	0·00
2	0·90	0·94	0·98	0·87	0·75	0·83	1·00	0·15	0·14
3	0·84	0·92	0·98	0·80	0·51	0·71	1·00	0·20	0·18
4	0·87	0·95	0·98	0·89	0·75	0·83	1·00	0·15	0·15
5	0·89	0·93	0·98	0·79	0·53	0·73	0·98	0·20	0·20
6	0·85	0·95	0·98	0·77	0·52	0·71	0·98	0·24	0·20
7	0·95	1·00	1·00	0·93	0·90	0·85	1·00	0·09	0·00
8	0·95	1·00	1·00	0·95	0·90	0·84	1·00	0·12	0·00
9	0·90	1·00	1·00	0·81	0·65	0·66	1·00	0·30	0·05
10	0·93	0·99	1·00	0·87 0·94	0·77 0·87	0·80 0·85	1·00	0·25 0·19	0·00
11	0·48	0·95	0·95	0·30	0·11	0·29 *	0·98	0·55	0·35
12	0·64	0·90	0·95	0·50	0·24	0·43	0·98	0·58	0·35
13	0·41 *	0·77	0·89	0·27 *	0·19 *	0·15	0·90	0·79	0·70
14	0·30 *	0·61	0·84	0·15 *	0·08 *	0·15	0·80	0·77	0·68
Tigogenin derivatives									
15	0·20	0·65	0·85	0·11 *	0·04 *	0·12	0·85	0·83	0·70
16	0·47	0·83	0·95	0·30	0·13	0·29	0·93	0·69	0·50
17	0·09	0·45	0·76	0·08 *	0·04 *	0·11 *	0·75	0·85	0·75
18	0·44	0·79	0·91	0·28	0·13	0·26 *	0·83	0·71	0·50
19	0·11 *	0·31*	0·57	0·06 *	0·04 *	0·12	0·89	0·87	0·60
20	0·10 *	0·34 *	0·59	0·04 *	0·04 *	0·03	0·47	0·90	0·83
21	0·15 *	0·55 *	0·73	0·10 *	0·04 *	0·13 *	0·83	0·84	0·66
22	0·09 *	0·30 *	0·51	0·08 *	0·04 *	0·12 *	0·52	0·88	0·82
23	0·09 0·18	—	0·73	0·06 0·11	0·06 *	0·11 *	0·70 0·80	0·77 0·66	0·70 0·46
24	0·11	0·45	0·71	0·08 *	0·04 *	0·08 *	0·73	0·83	0·74

* R_F value measured for the head of a streak; in other cases spots were well-defined circles.

11-Oxotigogenone (VIII), made in 66% and 78% yield respectively by similar oxidations of 11-oxotigogenin (VII) and 11β-hydroxytigogenone (VI) (see below), needles (from ether–hexane), m. p. 245—248°, $[\alpha]_D^{25}$ −16° (*c* 1·2), $\nu_{max.}$ 1710 cm.$^{-1}$, R_F 0·90 (lit.,[3] m. p. 236—238°, $[\alpha]_D^{20}$ −19°).

11α-*Hydroxytigogenin* (III).—11-Oxotigogenin acetate (VIIa) (2 g.)[43] was reduced[44] with

[43] (*a*) Schmidlin and Wettstein, *Helv. Chim. Acta*, 1953, **36**, 1241; (*b*) Cornforth, Osbond, and Phillipps, *J.*, 1954, 907.

[44] Heusser, Anliker, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 1537; Oliveto, Hershberg, *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 1505, and earlier papers.

sodium (20 g.) in refluxing propan-1-ol (400 ml.). The metal was added during 1 hr., and the solution refluxed for another 1·5 hr. The crystallised product (III) (1·59 g., 87%) occurred as rhombs, m. p. 220—222°, $[\alpha]_D^{26}$ −78° (*c* 0·91), R_F 0·35.

11α-*Hydroxytigogenin acetate* (IIIa) was made from the 3-alcohol (III) (0·74 g.), pure pyridine (5 ml.), and acetic anhydride (0·23 g., 1·3 equiv.), kept for 22 hr. at 0°. Chromatography of the product on alumina (Grade H) and crystallisation from acetone of the solid eluted with ether afforded the 3-*acetate* (IIIa) as needles (60 mg., 7%), m. p. 202—204°, $[\alpha]_D^{25}$ −74° (*c* 0·5), $\nu_{max.}$ 1730 and 1240 cm.$^{-1}$, R_F 0·73 (Found : C, 73·1; H, 9·9. $C_{29}H_{46}O_5$ requires C, 73·4; H, 9·8%). Methanol eluted a fraction (0·33 g.) identified as the original diol (III), acetylation of which with pyridine (2 ml.) and acetic anhydride (5 ml.) at 90—100° for 1 hr. gave the diacetate (IIIb), needles (from acetone–hexane), m. p. 173—175°, $[\alpha]_D^{27}$ −80° (*c* 0·64), $\nu_{max.}$ 1730 and 1238 cm.$^{-1}$, R_F 0·93.

11α-*Acetoxytigogenin* (IIIc).—A solution of the foregoing diacetate (IIIb) (0·8 g.) in methanol (34 ml.) containing potassium hydrogen carbonate (0·22 g., 1·4 equiv.) and water (4 ml.) was refluxed for 1·6 hr. The isolated product (0·77 g.) crystallised from acetone as needles of the 11-*acetate* (IIIc) (0·39 g., 53%), m. p. 175—178°, $[\alpha]_D^{18}$ −95° (*c* 0·85), $\nu_{max.}$ 1730 and 1240 cm.$^{-1}$, R_F 0·80 (Found : C, 73·6; H, 9·7. $C_{29}H_{46}O_5$ requires C, 73·4; H, 9·8%).

11-Oxotigogenin (VII) (made by hydrolysis of its 3-acetate [44]), rhombs (from acetone–hexane), m. p. 224—227°, $[\alpha]_D^{23}$ −34° (*c* 0·98), $\nu_{max.}$ 1705 cm.$^{-1}$, R_F 0·81 (lit.,[3] m. p. 223—225°, $[\alpha]_D^{20}$ −29°).

11β-*Hydroxytigogenin* (V).—Reduction of 11-oxotigogenin acetate (VIIa) (0·5 g.) in absolute ether (200 ml.) with lithium aluminium hydride (0·5 g.) in ether (100 ml.) (to which the steroid was added) was complete in 20 min. at the b. p.[3] Crystallisation from acetone of the isolated steroid [which gave a faint spot on a paper chromatogram in the position expected for the 3β : 11α-diol (III)] afforded prisms (3·44 g., 75%), m. p. 200—205°, $[\alpha]_D^{19}$ −53°. Recrystallisation gave the pure diol (V), m. p. 208—212°, $[\alpha]_D^{18}$ −56° (*c* 0·77), R_F 0·61 (lit.,[3] m. p. 202—204°, $[\alpha]_D^{20}$ −49°).

Reduction of the ketol acetate (VIIa) (5 g.) in refluxing alcohol (120 ml.) and water (20 ml.) containing potassium hydrogen carbonate (2 g.) and sodium borohydride (2·6 g.) was complete within 1·5 hr. The crude product appeared homogeneous (by paper chromatography), and crystallisation from acetone afforded the pure diol (V) (4·21 g., 92%). The derived acetate (Va) occurred as needles, m. p. 230—235°, $[\alpha]_D^{22}$ −63° (*c* 0·83), $\nu_{max.}$ 1735 and 1242 cm.$^{-1}$, R_F 0·86 (Found : C, 73·45; H, 9·6. Calc. for $C_{29}H_{46}O_5$: C, 73·4; H, 9·8%) (lit.,[3] m. p. 225—227°, $[\alpha]_D^{20}$ −47°, and [44] m. p. 222—224°, $[\alpha]_D^{20}$ −55°).

11β-*Acetoxytigogenin Acetate* (Vb).—The 3β : 11β-diol (V) (3·4 g.) in "AnalaR" benzene (50 ml.), toluene (25 ml.), *NN*-dimethylaniline (20 ml.), and acetyl chloride (6 ml.) was refluxed gently under nitrogen for 20 hr. Crystallisation from acetone of the isolated steroid afforded rhombs (3·76 g., 93%) of the 3β : 11β-*diacetate* (Vb), m. p. 102—106°. Recrystallisation gave the analytical specimen, m. p. 103—107°, $[\alpha]_D^{20}$ −38° (*c* 0·94), $\nu_{max.}$ 1732 and 1240 cm.$^{-1}$, R_F 0·91 (Found : C, 71·8; H, 9·6. $C_{31}H_{48}O_6$ requires C, 72·1; H, 9·4%).*

11β-*Acetoxytigogenin* (Vc), made by hydrolysis (1·5 hr.) of the foregoing diacetate (Vb) (3·2 g.) in refluxing methanol (90 ml.) and water (15 ml.) containing potassium hydrogen carbonate (2·5 g.), crystallised from acetone as needles (2·03 g., 69%), m. p. 208—210°. A recrystallised specimen had m. p. 214—215°, $[\alpha]_D^{24}$ −41° (*c* 1·02), $\nu_{max.}$ 1734 and 1240 cm.$^{-1}$, R_F 0·73 (Found : C, 73·5; H, 9·85. $C_{29}H_{46}O_5$ requires C, 73·4; H, 9·8%).

11β-*Acetoxytigogenone* (VIa).—11β-Acetoxytigogenin (Vb) (1·5 g.) in "AnalaR" acetone (80 ml.) was treated with *N*-bromoacetamide (1·0 g.) and set aside for 18 hr. at room temperature. Crystallisation from acetone of the isolated steroid gave needles (1·07 g., 72%), m. p. 185—192°. Two recrystallisations gave the pure *acetate* (VIa), m. p. 190—194°, $[\alpha]_D^{19}$ −31° (*c* 1·1), $\nu_{max.}$ 1732 and 1238, and 1715 cm.$^{-1}$, R_F 0·88 (Found : C, 73·8; H, 9·3. $C_{29}H_{44}O_5$ requires C, 73·7; H, 9·4%).

Oxidation of 11α-*Hydroxytigogenin* (III).—The diol (III) (0·155 g.) in acetone (5 ml.) was oxidised at room temperature with 1·33N-potassium dichromate in 5N-sulphuric acid (0·59 ml., 1·1 equiv.). After the oxidant had been used up, the steroid (0·165 g.), $[\alpha]_D^{23}$ −45°, was isolated.

* Callow and James (*J.*, 1956, 4739) give m. p. 141—142·5°, $[\alpha]_D^{21}$ −35°, for this compound, but have no specimen available for comparison. In a redetermination our material, now 2½ years old, had m. p. 134—136°, but its infrared absorption was unchanged. Isomorphism is probably responsible for the discrepancies.

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Paper chromatography showed that it consisted of a mixture of at least three compounds, probably the dione (VIII), 11-oxotigogenin (VII), and the original diol (III) (in order of increasing polarity). Chromatography on alumina (Grade H) afforded pure specimens (20, 30, and 30 mg.) of these compounds, eluted with benzene, ether, and chloroform respectively.

11α-*Hydroxytigogenone* (IV).—A solution of the diol (III) (1 g.) in " AnalaR " acetone (70 ml.) containing *N*-bromoacetamide (0·646 g., 2 equiv.) was set aside at room temperature for 18 hr. The isolated *ketol* (IV) (0·99 g.) crystallised from acetone as rods (0·8 g., 80%), m. p. 212—214°, $[\alpha]_D^{19}$ −64° (*c* 0·63), $\nu_{max.}$ 1714 cm.$^{-1}$, R_F 0·65 (Found: C, 75·2; H, 9·8. $C_{27}H_{42}O_4$ requires C, 75·3; H, 9·8%). 11α-*Acetoxytigogenone* (IVa) formed plates (from acetone–hexane), m. p. 185—189°, $[\alpha]_D^{19}$ −73° (*c* 1·0), $\nu_{max.}$ 1732 and 1240, and 1718 cm.$^{-1}$, R_F 0·93 (Found: C, 73·8; H, 9·35. $C_{29}H_{44}O_5$ requires C, 73·7; H, 9·4%).*

Oxidation of 11β-*Hydroxytigogenin* (V).—(i) *With* N-*bromoacetamide*. The diol (V) (0·5 g.) and *N*-bromoacetamide (0·323 g., 2 equiv.) were kept in " AnalaR " acetone (35 ml.) at room temperature for 16 hr. The crude product appeared by paper chromatography to contain the dione (VIII) and the 11-ketone (VII). Chromatography on alumina afforded a pure specimen (65 mg.) of the former (eluted with benzene); ether eluted material inert to Brady's reagent from which pure 11-oxotigogenin (VII) (0·10 g.) was obtained crystalline.

(ii) *With potassium dichromate*. The diol (V) (0·3 g.) in " AnalaR " acetone (10 ml.) at room temperature was oxidised with 1·33N-potassium dichromate in 5N-sulphuric acid (1·045 ml., 1·1 equiv.). The product (0·28 g.) seemed (by paper chromatography) to contain a trace of the original diol (V) with the ketol (VII) and dione (VIII). Chromatography on alumina (Grade H) afforded the last-named in the benzene eluate (0·115 g.); crystallisation afforded a pure specimen (55 mg.). Crystallisation of the material eluted by ether gave the 11-ketone (VII) (0·125 g.). The diol (V) was not isolable.

(iii) *Oppenauer method*. The 3β : 11β-diol (V) (2 g.) in toluene (80 ml.) and anhydrous *cyclo*hexanone (15 ml.) was refluxed with aluminium *iso*propoxide (1 g.) in toluene (10 ml.) for 1 hr., the solvents were distilled off with steam, and 11β-*hydroxytigogenone* was isolated with ethyl acetate and crystallised from methanol as prisms (1·28 g., 68%), m. p. 222—227°, $[\alpha]_D^{21}$ −45°. Recrystallised material had m. p. 225—228°, $[\alpha]_D^{20}$ −46° (*c* 0·91), $\nu_{max.}$ (in Nujol) 1694 cm.$^{-1}$, R_F 0·78 (Found: C, 75·1; H, 9·9. $C_{27}H_{42}O_4$ requires C, 75·3; H, 9·8%). The compound gave an immediate precipitate with Brady's reagent.

3-*Methylsarsasapogenin*.—Professor Barton having been kind enough to make available to us the late Professor Kon's collection of sapogenin specimens, we were able to examine samples of 3-methylsarsasapogenin. Although the action of methylmagnesium halides on 3-oxo-steroids generally gives mixtures of epimeric stanols, Farmer and Kon [42] reported no difficulty in isolating a product from sarsasapogenone that they pronounced " clearly homogeneous." Paper chromatography of two of Professor Kon's specimens of 3-methylsarsasapogenin revealed two components in each: the higher-melting specimen predominated in the component with the higher R_F value and the other contained the two in nearly equal amounts. We examined the infrared absorption with Dr. Page's help. Although the spirostan system introduces absorption in the 1000—1100 cm.$^{-1}$ region overlying the relatively weak bands due to the C–O frequencies in the carbinol groups, the lower-melting specimen showed a peak at 1028 cm.$^{-1}$, probably attributable to a 3β(axial)-hydroxyl group, and the other a peak at 1060 cm.$^{-1}$, befitting the absorption of the equatorial 3α-hydroxyl group.[45] Supplies of these materials were too exiguous for further work; therefore we can presume only that the components are the epimeric 3α-hydroxy-3β-methyl- and 3β-hydroxy-3α-methyl-spirostan. If so, then the latter epimer is the less hydrophilic, notwithstanding the equatorial configuration of its hydroxy-group.

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[45] Rosenkrantz *et al.*, *J. Biol. Chem.*, 1952, **195**, 503, 509; *J. Amer. Chem. Soc.*, 1953, **75**, 903; 1955, **77**, 2237; Furst, Kuhn, Scotoni, and Günthard, *Helv. Chim. Acta*, 1952, **35**, 951; Cole, Jones, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 5571; cf. Dauben, Hoerger, and Freeman, *ibid.*, p. 5206; Cole, *J.*, 1952, 4969.

231. *Palladium*(0) *Compounds. Part II.*[1] *Compounds with Triarylphosphines, Triaryl Phosphites, and Triarylarsines.*

By L. Malatesta and (Miss) M. Angoletta.

The preparation of a number of complex compounds of zero-valent palladium with phosphorus donors is described. They can be prepared from $Pd(R{\cdot}NC)_2$ and donor, or by reduction of palladium(II) compounds in the presence of excess of donor.

Three types of complexes have been isolated : $(R{\cdot}NC)(L)_3Pd$, PdL_4, and PdL_3 (L = triarylphosphines and triaryl phosphites). The compounds PdL_4 are largely dissociated in solution.

The triphenylarsine complex $(Ph_3As)_4Pd$ has also been obtained.

Previously we mentioned [1] the reaction between di*iso*cyanopalladium(0) and tri-*p*-chlorophenyl phosphite which yielded a mixed phosphite–*iso*cyanide complex. This is a general reaction, and is shown by triaryl phosphites, triarylphosphines, and triarylarsines. Its course, however, varies with the *iso*cyanide which forms complexes with palladium(0) and the substituting ligand (*e.g.*, phosphines, arsines, and various *para*-substituted triphenyl phosphites). The resulting products, all derivatives of palladium(0), can be classed into three groups.

(1) iso*Cyano–Triphosphite–Palladium*(0) *Compounds.*—The reaction described previously [1] belongs to this class :

$$(p\text{-}CH_3{\cdot}C_6H_4{\cdot}NC)_2Pd + 3(p\text{-}Cl{\cdot}C_6H_4{\cdot}O)_3P = (p\text{-}CH_3{\cdot}C_6H_4{\cdot}NC)[(p\text{-}Cl{\cdot}C_6H_4{\cdot}O)_3P]_3Pd$$

A similar product is also obtained from triphenyl phosphite with di-*p*-methoxyphenyl*iso*cyanopalladium. These products, in view of the similarity in behaviour of *iso*cyanides and carbon monoxide, can be considered analogous to the carbonyltristriaryl phosphite-nickel(0) compounds already described,[2] *e.g.*, $(CO)[(C_6H_5O)_3P]_3Ni$.

(2) *Symmetrical Tetrasubstituted Palladium*(0) *Compounds.*—The action of triphenyl phosphite on di-*p*-tolyl*iso*cyanopalladium(0) and that of triphenylphosphine and triphenylarsine on di-*p*-methoxyphenyl*iso*cyanopalladium(0) lead to the complete loss of *iso*cyanide with the formation of a symmetrically tetrasubstituted compound in which the metal is co-ordinatively saturated :

$$(p\text{-}CH_3{\cdot}C_6H_4{\cdot}NC)_2Pd + 4(C_6H_5O)_3P = [(C_6H_5O)_3P]_4Pd + 2p\text{-}CH_3{\cdot}C_6H_4{\cdot}NC$$

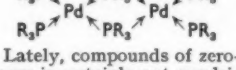
However, reactions of triarylphosphines and triaryl phosphites with nickel carbonyl do not give the analogous symmetrically tetrasubstituted compounds of nickel.

Tetrasubstitution occurs only with the chloro-derivatives of phosphorus(III), *e.g.*, $(C_6H_5{\cdot}PCl_2)_4Ni$, $(C_6H_5O{\cdot}PCl_2)_4Ni$,[2] and $(PCl_3)_4Ni$.[3] It is noteworthy that $Ni(PF_3)_4$, which resembles $Ni(CO)_4$, cannot be obtained by direct replacement of the carbon monoxide from the carbonyl itself; the substitution stops after the introduction of three PF_3 molecules, and the tetrakistrifluorophosphorus(III) compound has to be prepared by fluorination of $Ni(PCl_3)_4$.[3]

(3) *Symmetrically Trisubstituted Palladium*(0) *Compounds.*—When tri-*p*-chlorophenylphosphine reacts with di-*p*-tolyl*iso*cyanopalladium(0) both *iso*cyanide molecules are eliminated with formation of a trisubstituted compound which is co-ordinatively unsaturated * and has no equivalent in the series of nickel complexes :

$$(p\text{-}CH_3{\cdot}C_6H_4{\cdot}NC)_2Pd + 3(p\text{-}Cl{\cdot}C_6H_4)_3P = [(p\text{-}Cl{\cdot}C_6H_4)_3P]_3Pd + 2p\text{-}CH_3{\cdot}C_6H_4{\cdot}NC$$

* A referee suggests that the compounds of the type $(PR_3)_3Pd$ could be dimeric and formulated as :



In our opinion this is very unlikely. Lately, compounds of zero-valent platinum $(PR_3)_2Pt$, have been prepared by one of us, in which platinum is certainly not quadricovalent, and this may be taken as an indirect proof for our formulation.

[1] Part I, Malatesta, *J.*, 1955, 3924.
[2] Malatesta and Sacco, *Ann. Chim., Italy*, 1954, **44**, 134.
[3] Wilkinson, *J. Amer. Chem. Soc.*, 1951, **73**, 5501.

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The formation of stable co-ordinatively unsaturated compounds of palladium(0) had already been observed, *e.g.*, with *iso*cyanides as ligands, and could be foreseen from a consideration of the different behaviour of Pd(II) and Ag(I) [which is isolectronic with Pd(0)]. Trico-ordination with uncharged ligands is uncommon but has been recently observed in phosphine complexes of Ag(I).[4]

This tendency to co-ordinative unsaturation is also supported by the fact that the tetraco-ordinated complexes, *e.g.*, $(Ph_3P)_4Pd$, are largely dissociated in benzene.*

Three other methods of preparation of the compounds of classes (2) and (3), *i.e.*, those not containing *iso*cyanides, have been developed. These start from derivatives of palladium(II) and (with only one exception) give exclusively tetraco-ordinated palladium(0) compounds—the exception is the complex of tri-*p*-tolylphosphine which is trico-ordinated : $[(p\text{-}CH_3\cdot C_6H_4)_3P]_3Pd$. These methods are : (i) The action of hydrazine on an alcoholic suspension of bistriarylphosphinedihalogenopalladium in the presence of excess of phosphine, *e.g.*,

$$2(Ph_3P)_2PdCl_2 + 4R_3P + 5H_2N\cdot NH_2 = 2(R_3P)_4Pd + 4H_2N\cdot NH_2,HCl + N_2$$

This reaction is of fairly general application and has given positive results in some cases where methods (ii) and (iii) failed.

(ii) The action of excess of triarylphosphine or triaryl phosphite, in concentrated alcoholic solution, on freshly precipitated palladium oxide :

$$PdO + 5(RO)_3P = [(RO)_3P]_4Pd + (RO)_3PO$$

This reaction gives good results with triphenylphosphine and triphenyl phosphite, but with tri-*p*-tolylphosphine and tri-*p*-chlorophenyl phosphite there is direct reduction of palladium oxide to the metal.

(iii) The reaction of excess of triphenylphosphine or triphenyl phosphite with a hot, concentrated solution of palladium(II) nitrate :

$$Pd(NO_3)_2 + 9R_3P = (R_3P)_4Pd + N_2O + 5R_3PO$$

This method has approximately the same applicability as method (ii), but requires a larger excess of ligand.

It is noteworthy that the autoreduction of palladium(II) to palladium(0) in palladous oxide and nitrate can be correlated with the well-known fact that phosphines, phosphites, and arsines can form complexes with almost comparable stabilities with metals in different oxidation states [Ni(IV),[5] Ni(III),[6] Ni(II), Ni(0), Pd(II), Pd(0), etc.] but only rarely give co-ordination compounds with highly charged cations. In the above reaction one can assume that the hypothetical cation $(Pr_3P)_4Pd^{2+}$, which cannot be isolated, easily forms the uncharged complex with the metal in a formally zero-valent state. The complex with triphenylarsine could be obtained only by the action of this ligand on the di*iso*cyano-palladium(0) compound. It is reasonably stable to aerial oxidation, but we could not purify the complex because the solvents that dissolve it cause decomposition.

The compounds prepared, their decomposition temperature, and colour are given in the Table.

* From molecular-weight determination in this solvent it appears to be largely dissociated, and to account for the very low figures obtained one must assume that a dico-ordinated complex is present in solution :

$$(Ph_3P)_4Pd \longrightarrow (Ph_3)_3Pd + Ph_3P$$
$$(Ph_3P)_3Pd \longrightarrow (Ph_3)_2Pd + Ph_3P.$$

[4] Cass, Coates, and Hayter, *J.*, 1955, 4007.
[5] Nyholm, *J.*, 1951, 2602.
[6] Jensen, *Z. anorg. Chem.*, 1936, **229**, 265.

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Complex	Decompn. temp.	Colour
(*p*-MeO·C_6H_4·NC)[(*p*-Cl·C_6H_4)$_3$P]$_3$Pd	90—100°	colourless
(*p*-MeO·C_6H_4·NC)[(*p*-Cl·C_6H_4·O)$_3$P]$_3$Pd	100—105	colourless
(*p*-MeO·C_6H_4·NC)[(PhO)$_3$P]$_3$Pd	105—110	colourless
$(Ph_3P)_4Pd$	100—105	yellow
[(*p*-Cl·C_6H_4)$_3$P]$_4$Pd	120—160	lemon-yellow
[(Ph·O)$_3$P]$_4$Pd	120—130	colourless
$(Ph_3As)_4Pd$	80—100	colourless
[(*p*-Cl·C_6H_4)$_3$P]$_3$Pd	90—100	yellow
[(*p*-CH_3·C_6H_4)$_3$P]$_3$Pd	110	golden-yellow

Experimental

p-*Methoxyphenyl*iso*cyanotristri*-p-*chlorophenylphosphinepalladium*.—Di-*p*-methoxyphenyliso-cyanopalladium (0·74 g.; 2 mmoles) and tri-*p*-chlorophenylphosphine (2·92 g.; 8 mmoles) were heated in benzene (8—10 c.c.). The solution was filtered from the solid residue and anhydrous ethanol added. The product thus precipitated cannot be purified (Found: Pd, 8·3; P, 7·3; Cl, 25·6; N, 1·2. Calc. for $C_{62}H_{43}ONCl_9P_3Pd$: Pd, 7·95; P, 7·0; Cl, 23·9; N, 1·05%).

p-*Methoxyphenyl*iso*cyanotris*(*tri*-p-*chlorophenyl phosphite*)*palladium* was prepared analogously, and purified by recrystallization from ethanol (Found: Pd, 7·05; P, 6·5; N, 1·0. $C_{62}H_{43}O_{10}NCl_9P_3Pd$ requires Pd, 7·2; P, 6·3; N, 0·95%).

p-*Methoxyphenyl*iso*cyanotris*(*triphenyl phosphite*)*palladium* was prepared and purified analogously (Found: Pd, 9·2; P, 8·1; N, 1·3. $C_{62}H_{52}O_{10}NP_3Pd$ requires Pd, 9·1; P, 7·9; N, 1·2%).

Tetrakistriphenylphosphinepalladium.—Powdered palladium nitrate (2 mmoles) was treated with triphenylphosphine (approx. 20 mmoles) in hot benzene (10 c.c.). After a vigorous reaction with the evolution of much nitrous oxide a solid mass was obtained on cooling. The crude *product* was recrystallized from ethanol. It is stable to air for only a short time and on prolonged exposure turns from yellow to orange [Found: Pd, 9·2; C, 75·1; H, 5·2; P, 10·4%; *M*, cryoscopic in benzene (0·601 g./20 c.c.), 355. $C_{72}H_{60}P_4Pd$ requires Pd, 9·1; C, 74·9; H, 5·2; P, 10·5%; *M*, 1156). From the mother-liquor of the recrystallization Ph_3PO, m. p. 154° (1·5 g. from 5 g. of Ph_3P), was recovered.

Tetrakistri-p-*chlorophenylphosphinepalladium*.—Finely powdered bistri-*p*-chlorophenylphosphinedichloropalladium (2 g.; 2·5 mmoles) (obtained by treating an alcoholic solution of H_2PdCl_4 with the phosphine) and tri-*p*-chlorophenylphosphine (1·8 g.; 5 mmoles) were suspended in anhydrous ethanol and a 10% alcoholic solution of hydrazine hydrate added dropwise. The yellow crystalline *product* was repeatedly washed with hot chloroform (10—15 c.c.) and the filtrate collected in cold anhydrous ethanol (100 c.c.); the solid formed was filtered off and dried. It is insoluble in alcohol and soluble in chloroform and benzene (Found: Pd, 6·6; P, 8·1; Cl, 26·9. $C_{72}H_{48}Cl_{12}P_4Pd$ requires Pd, 6·8; P, 7·9; Cl, 27·2%).

Tetrakis(*triphenyl phosphite*)*palladium*.—Di-*p*-tolyliso*cyanopalladium (0·68 g.; 2 mmoles), triphenyl phosphite (2·48 g.; 8 mmoles), and benzene (10—15 c.c.) were heated for a few minutes, the benzene was evaporated under reduced pressure, and the residue washed with alcohol, then recrystallized from this solvent, from which it was obtained as white *needles* [Found: Pd, 7·85; P, 9·4%; *M*, cryoscopic in benzene (0·731 g./20 c.c.), 380. $C_{72}H_{60}O_{12}P_4Pd$ requires Pd, 7·9; P, 9·2%; *M*, 1347].

Tetrakistriphenylarsinepalladium.—Di-*p*-tolyliso*cyanopalladium (0·36 g.; 1 mmole), triphenylarsine (1·84 g.; 6 mmoles), and ethanol (*ca.* 10 c.c.) were warmed on a water-bath for 15—20 min. After cooling, the crystalline precipitate was filtered off and washed on the filter with light petroleum. It could not be further purified, but the crude *product* does not contain nitrogen (Found: Pd, 7·6; As, 21·3. $C_{72}H_{60}As_4Pd$ requires Pd, 8·0; As, 22·5%).

Tristri-p-*chlorophenylphosphinepalladium*.—Di-*p*-tolyliso*cyanopalladium (0·67 g.; 2 mmoles), tri-*p*-chlorophenylphosphine (4·36 g.; 12 mmoles), and toluene (5—6 c.c.) were heated for 10—15 min. The *product* was purified by dissolving it in benzene and reprecipitating with ethanol (Found: Pd, 8·7; P, 7·8. $C_{54}H_{36}Cl_9P_3Pd$ requires Pd, 8·85; P, 7·7%).

Tristri-p-*tolylphosphinepalladium* was prepared analogously from [(*p*-CH_3·C_6H_4)$_3$P]$_2$$PdI_2$ (1·5 g.; 1·55 mmoles), tri-*p*-tolylphosphine (1·52 g.; 5 mmoles), and hydrazine hydrate. It turns brown on exposure to air (Found: Pd, 10·0; P, 9·3. $C_{63}H_{63}P_3Pd$ requires Pd, 10·5; P, 9·1%).

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Istituto di Chimica Generale dell'Università di Milano. [*Received, September 27th*, 1956.]

232. *The Stereoisomerism of Addition Polymers. Part II.* Configurations of Maximum Order from Alternating Copolymerisation. The Requirements for Optical Activity in Polymers.*

By C. L. Arcus.

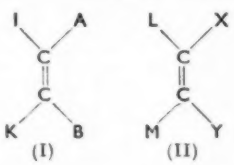
Configurations for linear alternating copolymers containing asymmetric carbon atoms have been deduced from a consideration of steric factors in initiation, propagation, and termination.

The steric effects of the use of optically active monomers in polymerisation are discussed, together with the conditions for the formation of a polymer having an optically active main chain.

The configuration of a growing ethylenic-addition chain molecule, derived from a single monomer, has been shown in Part I to be dependent on three factors: (*a*) the geometrical type of addition; in any individual polymerisation it is assumed that reaction is either *trans* at every step or *cis* at every step; (*b*) the attack by the initiating radical or ion, which may be at either side of the monomer molecule; the enantiomeric adducts so formed lead to enantiomeric chains, designated *D* and *L*; (*c*) the mode of presentation of the monomer to the chain-end; for all types of monomer, except those which are axially symmetrical, there are two alternative modes, represented in formulæ (IV—VII) of Part I. The operation of these factors in alternating copolymerisation is now considered, and configurations for alternating copolymers are derived. Complete alternation in copolymerisation implies that both monomer reactivity ratios approach zero, and, whereas the assessment of the stereoisomerism of copolymers formed where these ratios are larger numbers probably requires statistical methods, configurations of maximum order for alternating copolymers can be derived relatively simply.

Relevant experimental results have become available in two recent reports,[1,2] discussed in Section (2) below, on copolymerisations involving optically active monomers.

(1) *Configurations of Alternating Copolymers.*—The alternation of two monomers necessitates taking into account the presentation of each to the other. The two possible



(I) (II)

$$\begin{array}{cc}\text{I A}\\ \text{K B}\end{array}\!\!\!

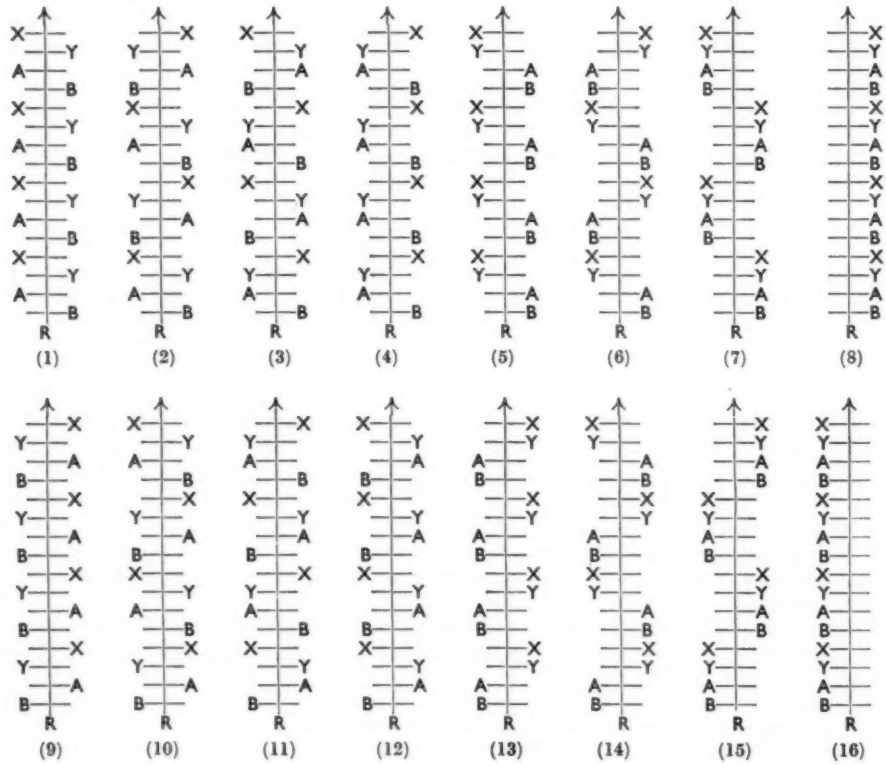
that of (I) to (II). Each presents two alternatives, and sixteen configurations, represented in Fischer formulæ (1—16), arise as follows:

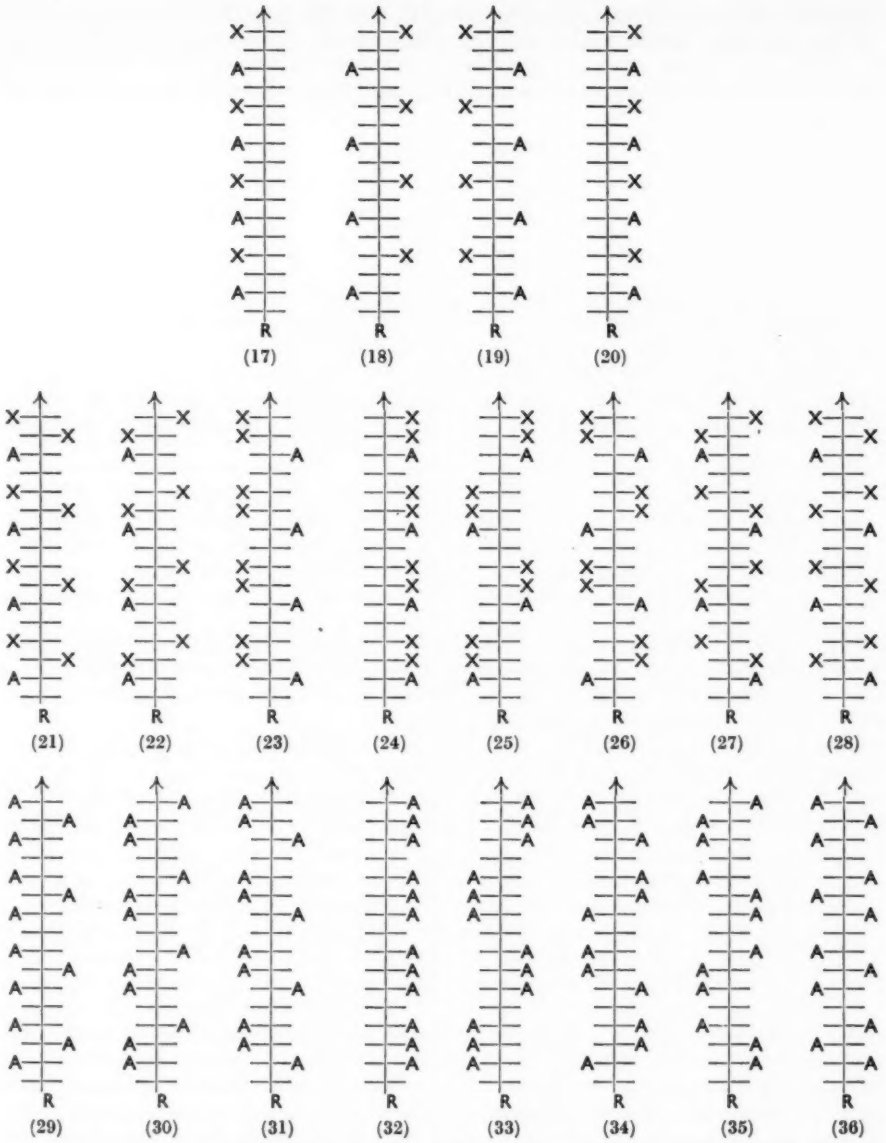
Addition	Presentation of (II) to (I)	Presentation of (I) to (II)	*D*-Initiation	*L*-Initiation
trans	[2]	[3]	(1)	(9)
trans	[2]	[3′]	(2)	(10)
trans	[2′]	[3]	(3)	(11)
trans	[2′]	[3′]	(4)	(12)
cis	[2]	[3]	(5)	(13)
cis	[2]	[3′]	(6)	(14)
cis	[2′]	[3]	(7)	(15)
cis	[2′]	[3′]	(8)	(16)

For greater clarity the groups I, K, L, M, have been omitted from (1—16), and, in the derived configurations, hydrogen has likewise been omitted.

On inspection of the chains (1—16) from their points of initiation, it is apparent that there are eight pairs of enantiomers, each pair diastereoisomeric with the others. When sections of these chains, of indefinite length and remote from end-groups, are considered, it is apparent that none possesses a plane of symmetry, but that (2) and (10) are identical, as are (3) and (11), (6) and (14), (7) and (15).

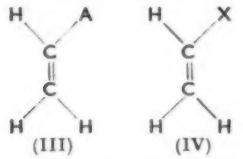
Configurations for copolymers of less-substituted ethylenic monomers have been derived by simplification of (1—16). It has been necessary to take into account the tendency of groups, on the chain-end and the approaching monomer, to associate or to repel; however, the forces on which these tendencies depend, *e.g.*, electrostatic, steric, and resonance interactions, and hydrogen bonding, of which the applicability will vary with the nature of the monomer, are not discussed.





Copolymerisation of CH_2:CHA *and* CH_2:CHX. Monomers (I) and (II) are replaced by (III) and (IV), and [2], [2′], [3], [3′], become [4], [4′], [5], [5′]. However, if [4], in which X is relatively close to A, is appropriate for the presentation of (IV) to (III), then [5], not [5′], is probable for the presentation of (III) to (IV); similarly, if [4′], in which X and A are relatively remote, is appropriate, then [5′], not [5], is probable; *i.e.*, the application of the general case is to be limited in that [2] is here coupled with [3], and [2′] with [3′]. The configurations derived from (1), (4), (5), (8), (9), (12), (13), (16), are, therefore, more probable than those derived from the remaining forms; these configurations lead to only

four different configurations: (1), (16) ⟶ (17); (4), (13) ⟶ (18); (5), (12) ⟶ (19); (8), (9) ⟶ (20). Of these, (17) and (20), (18) and (19), are enantiomers. When non-terminal sections of the chains are compared, it is found that each has a plane of symmetry at every substituted carbon atom, and that (17) and (20) are identical, as are (18) and (19).

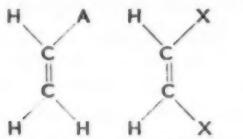


(III) (IV)

[4]	[4′]	[5]	[5′]
H X	X H	H A	A H
H H	H H	H H	H H
H A	H A	H X	H X
H H	H H	H H	H H

The copolymerisation of CH_2:CIA and CH_2:CHX involves a consideration of presentation similar to that above; the configurations derived from this copolymerisation are (17—20), except that the groups >CHA are replaced by >CIA.

Copolymerisation of CH_2:CHA *and* cis-CHX:CHX. Monomers (I) and (II) are replaced by (III) and (V), and the presentations for this copolymerisation are given by [6], [6′], [7], [7′]. From considerations similar to those above, [6] would be expected to be coupled

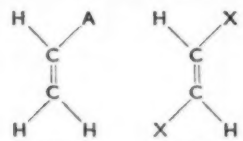


(III) (V)

[6]	[6′]	[7]	[7′]
H X	X H	H A	A H
H X	X H	H H	H H
H A	H A	H X	H X
H H	H H	H X	H X

with [7], and [6′] with [7′]. There arise four *D*- and four *L*-chain configurations, derived respectively from (1), (4), (5), (8), and (9), (12), (13), (16); the *D*-forms are represented in (21—24). Non-terminal sections of all these chains have no plane of symmetry, and sections of enantiomers are nowhere identical.

Copolymerisation of CH_2:CHA *and* trans-CHX:CHX. Monomers (I) and (II) are replaced by (III) and (VI); the presentations are given by [8], [8′], [9], [9′]. If, as in [8], the groups A and the lower X are relatively remote as the monomer molecule (VI) approaches the chain end, then [9′] is the more probable presentation for the addition of



(III) (VI)

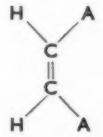
[8]	[8′]	[9]	[9′]
H X	X H	H A	A H
X H	H X	H H	H H
H A	H A	H X	H X
H H	H H	X H	X H

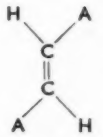
(III). Conversely, if these groups are relatively close, as in [8′], then [9] is the more probable; *i.e.*, in the application of the general case, [2] is to be coupled with [3′], and [2′] with [3], whence forms (2), (3), (6), (7), and (10), (11), (14), (15), are applicable; they lead to four *D*- and four *L*-configurations, the *D*-forms being represented in (25—28). Non-terminal sections of these chains have no plane of symmetry, but sections of enantiomers are identical.

Configurations for the copolymerisation of CH_2:CIA with *cis*- and with *trans*-CHX:CHX are (21—24) and (25—28), and enantiomers, except that the groups >CHA are replaced by >CIA.

Copolymerisation of CH_2:CHA *and* cis-CHA:CHA. The derivation of the configurations is the same as that for the copolymerisation of CH_2:CHA and *cis*-CHX:CHX, except that (V) is replaced by (VII); four *D*- and four *L*-configurations arise, of which the *D*-forms are represented in (29—32). Non-terminal sections of the chains possess the following

symmetry properties: (29) and (32), each of which is identical with its enantiomer, have a plane of symmetry at every CH_2-group and at the mid CHA-group in the sets of three; (30) and (31) are not identical with the corresponding enantiomers, and have no plane of symmetry. However, such sections of (30) and the enantiomer of (31) are identical, and *vice versa*.

(VII) 

 (VIII)

Copolymerisation of CH_2:CHA *and* trans-CHA:CHA. The configurations are derived as for the copolymerisation of CH_2:CHA with *trans*-CHX:CHX, except that (VI) is replaced by (VIII); four *D*- and four *L*-configurations arise, of which the *D*-forms are represented in (33—36). Non-terminal sections of these chains have the following symmetry properties: (33) and (36), each of which is identical with its enantiomer, have a plane of symmetry at every mid CHA-group in the sets of three; (34), (35), and their enantiomers, are all of one chain configuration which, however, has no plane of symmetry.

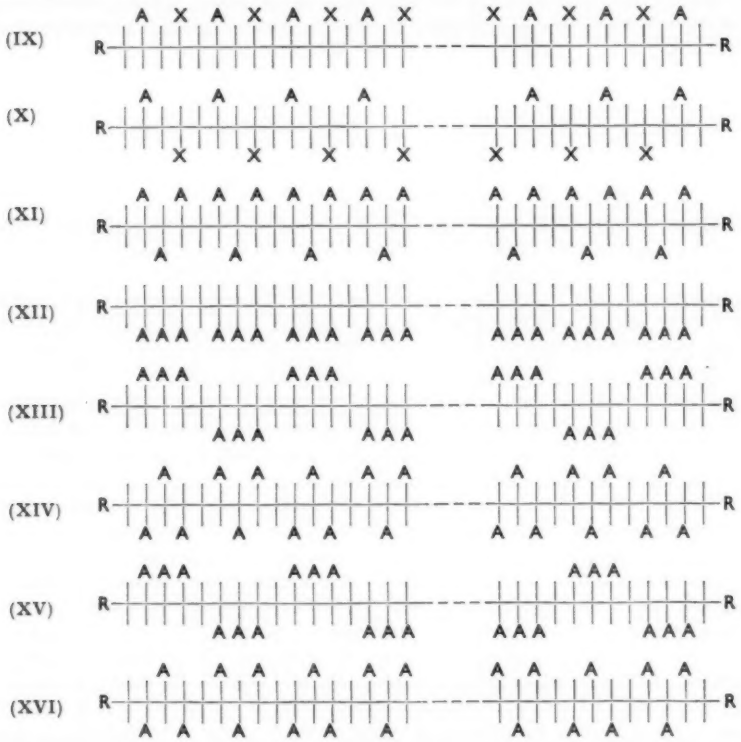
Termination and stereoisomerism. Formation of meso*-type chain molecules in copolymerisation.* With respect to their steric effects, mechanisms of termination fall into two classes (Part I): the simple terminations, which yield a molecule comprised of one of the chains, above, together with a relatively small terminating group, and mutual chain termination. The symmetry properties of simply terminated molecules are substantially those of non-terminal portions of the chains, which have been described above.

It has been shown (Part I) that in certain instances mutual chain termination results in the formation of *meso*-type chain molecules. By a *meso*-type of chain molecule is meant one in which (if irregularities at the point of juncture are ignored) the same "pattern" is apparent throughout the chain, and there are numerous "local" planes of symmetry. Examples are (XIV) and (XV) of Part I, and (IX—XVI) below. Such molecules arise by mutual termination in systems containing enantiomeric growing chains which themselves possess planes of symmetry; the act of termination produces a tail-to-tail unit which is, usually, a steric irregularity, and combination between two chains of like initiation (both *D* or both *L*) gives rise to an uncompensated unit at one end of the completed chain; when chains of unlike initiation combine, the chain ends are symmetrically disposed. If the chain configuration alternates, with identical sequences of groups to right and to left along the axis of the Fischer projection formula, then all mutual terminations give *meso*-type molecules; if such alternation is not present, then only $(D + L)$ terminations yield these molecules. Of the possible mutual terminations, $(D + D)$, $(L + L)$, $(D + L)$, the first two are enantiomerically related and must occur with equal frequency, but the last is in a diastereoisomeric relationship to the other two, and its frequency is not necessarily given by the random collision ratio of 1 : 1 : 2.

(If enantiomeric chains of exactly the same length combine, a molecule is formed which is *meso* in the classical meaning of the word, irrespective of the presence of planes of symmetry in the individual chains. However, this is an event of low probability, and such molecules will form only a small fraction of the whole product.)

No *meso*-type chain molecules are derived from the following configurations and their enantiomers, since they contain no planes of symmetry: (21—28), (30), (31), (34), (35), nor are such molecules given by combination between chains of like initiation in systems containing (17 + 20), (18 + 19), (29 + enantiomer), (32 + enantiomer). *meso*-Type molecules are formed by combination of chains of unlike initiation in these last four systems, and in (33 + enantiomer) and (36 + enantiomer), in both of which *meso*-type molecules are also formed by combination of chains of like initiation. The molecules so formed are respectively exemplified in (IX—XVI). Since they are derived from the same two systems,

in the manner described, (XV) and (XVI) differ from (XVIII) and (XIX) only in possessing an uncompensated unit at one end of the molecule.



(2) *Polymerisation and Copolymerisation of Optically Active Monomers.*—Several investigations in this field have now been reported, and a comparison of the results with the configurations above, and of Part I, is made in the present Section. The experimental procedures all involve the polymerisation or copolymerisation of a monomer in which an ethylenic group is attached to an optically active group, followed by removal of the latter groups and measurement of the rotatory power of the remaining polymer or copolymer. These investigations present two aspects: the influence of the optically active groups on the course of the polymerisation, and the extent to which the polymer structure, after removal of these groups, is capable of existence in a dissymmetric, optically active form.

The effects of the use of an optically active monomer on the course of polymerisation are considered to be as follows: (*a*) When such a monomer is the first unit of a growing chain, then either *D*- or *L*-initiation occurs preferentially, since the adducts of the monomer and the initiating radical or ion [(II) and (III) of Part I] are no longer optical isomers, but diastereoisomers, and will differ in rate of formation. (*b*) In the derivation of chain configurations, it is considered that a monomer which possesses a plane of symmetry through the σ-bond system [*e.g.*, (I) or (II)] presents a certain side of the molecule to a growing *D*-chain end, or, with equal facility, the other side to a growing *L*-chain end. With a monomer which does not possess such a plane of symmetry this equality is absent: the transition states comprised of the monomer (of, *e.g.*, configuration *d*), and polymer main chains of configurations *D* and *L*, become diastereoisomeric, *d*-*D* and *d*-*L*, and the rates of reaction and hence of chain growth will, in general, be different. (*c*) A further

element of dissymmetry is contributed to the transition states by the incorporation, in the growing chains, of optically active side groups, which render the chains themselves no longer optically isomeric, but diastereoisomeric.

Thus the factors (*a*), (*b*), (*c*) so operate that two enantiomeric main chains are not initiated or propagated at equal rates. Further, it has been envisaged (Part I) that, at intervals, a monomer molecule may be added irregularly, either as regards *trans*- or *cis*-addition, or with regard to mode of presentation; when such dislocations occur in polymerisations involving optically active monomers, the dissymmetric factors, as in (*b*) and (*c*), will assist the propagation of one chain configuration rather than the other.

Thus the presence of optically active groups in the molecules of a monomer can potentially give rise to a polymer the main chain of which is optically active; whether the polymer or copolymer remaining after the removal of the optically active side groups is in fact optically active, or not, would be expected to depend on the absence or presence of planes of symmetry in the chains so formed.

Three examples of polymerisation of optically active monomers CH_2:CHA or CH_2:CIA, with subsequent removal of the active groups, have been recorded: Marvel and Overberger [3] polymerised (+)-*sec.*-butyl *p*-vinylbenzoate, hydrolysed the polymer, and obtained optically inactive poly-(*p*-vinylbenzoic acid); Overberger and Palmer [1] polymerised (+)-*o*-(*sec.*-butylthiomethyl)styrene, quantitatively removed sulphur (and therefore the *sec.*-butyl groups) from the polymer by catalytic hydrogenation, and obtained an optically inactive polymer; Beredjick and Schuerch [2] polymerised (−)-1-phenylethyl methacrylate, removed the phenylethyl groups by reduction with phosphonium iodide, and obtained optically inactive poly(methacrylic acid). The configurations which have been deduced for the polymerisation of CH_2:CHA (or CH_2:CIA), (9—12) of Part I, all contain numerous local planes of symmetry, in accord with the absence of optical activity in the final polymers above.

Overberger and Palmer [1] also copolymerised (+)-*o*-(*sec.*-butylthiomethyl)styrene with methyl methacrylate, obtaining a copolymer which contained 0·43 mole-fraction of the former monomer; scission, as above, of the *sec.*-butyl groups yielded an optically inactive copolymer. There is no evidence on the degree of alternation in this copolymer, but it is of interest to compare the configurations, (17—20) above, for the alternating copolymer which is most closely related. These configurations all contain numerous local planes of symmetry, whence they are incapable of existing in an optically active form, and it is possible that the structure of the above copolymer is sufficiently similar to be essentially symmetrical.

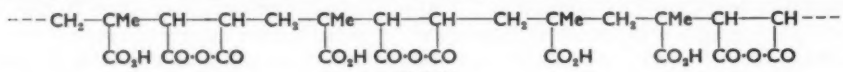
The preparation of a copolymer, the main chain of which was optically active, has been reported by Beredjick and Schuerch: [2] a partial asymmetric synthesis was effected by the copolymerisation of (−)-1-phenylethyl methacrylate with maleic anhydride, followed by removal of the phenylethyl groups by reduction with phosphonium iodide.

The reality of the asymmetric synthesis is to be accepted with some reserve, since the hydrogen content of the final copolymer (7·2%) is in 49% excess of the calculated value (4·85%). A partial asymmetric synthesis effected by hydrogenation has been reported,[4] and it does not seem impossible that some structure in the copolymer may have been reduced asymmetrically before complete removal of the 1-phenylethyl groups. However, the asymmetric synthesis being accepted, the steric structure of the copolymer can, in part, be estimated.

The (−)-1-phenylethyl methacrylate–maleic anhydride copolymer contained these units in ratio 1·5 : 1, whence the copolymer is not strictly alternating. The monomer reactivity ratios [5] for the copolymerisation of methyl methacrylate (M_1) and maleic anhydride (M_2) are: $r_1 = 6·7$ and $r_2 = 0·02$. Probably, therefore, in the above copolymer,

[3] Marvel and Overberger, *J. Amer. Chem. Soc.*, 1946, **68**, 2106.
[4] Arcus and Smyth, *J.*, 1955, 34.
[5] de Wilde and Smets, *J. Polymer Sci.*, 1950, **5**, 253.

a maleic anhydride unit is almost always followed by a methacrylate unit, but the converse does not necessarily hold, though steric hindrance between 1-phenylethyl groups might be expected to reduce r for 1-phenylethyl methacrylate below the value for methyl methacrylate. The structure of the reduced copolymer is exemplified in (XVII). Of the



(XVII)

chain configurations for alternating copolymerisation, forms (21—24), together with their *L*-enantiomers, are most closely related to (XVII). Pairs of groups X, in these configurations, represent the anhydride bridges, and groups A the carboxyl groups of the methacrylic acid units; the joining of pairs of groups X in a ring does not affect the configurations; also, were the anhydride rings hydrolysed to pairs of carboxyl groups, the carbon atoms bearing the carboxyl groups of the methacrylic acid units would remain distinguishable by the attached methyl groups. These configurations, which cover all the variations in mechanism which have been envisaged above, possess no planes of symmetry, and are therefore intrinsically capable of existing in optically active forms. If it be assumed that *trans*-addition occurs (Part I) and that the carbonyl groups of anhydride and ester tend to repel each other, leading to presentations [6′] and [7′], where A = CO·O·CHMePh, and the pairs of groups X = CO·O·CO, then configuration (22) or its enantiomer approximates most closely to this copolymer.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, October 16th*, 1956.]

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233. *The Analysis of Mixtures of Benzene-carboxylic Acids by Partition Chromatography.*

By BRIAN FISHWICK.

A method has been devised for the separation, by partition chromatography, of mixtures containing benzene-carboxylic acids, which allows identification and quantitative estimation of the component acids. A column of silica gel, with 0·5N-sulphuric acid as stationary phase, is used. Values of peak effluent volumes are reported for all benzene-carboxylic acids, except terephthalic acid. Methods for the preparation of all the less common benzene-carboxylic acids are described briefly.

DURING investigation into the chemical constitution of different coal macerals, it became necessary to identify and estimate individual benzene-carboxylic acids from the complex mixture obtained by oxidation of coals.[1] Partition chromatography seemed to offer the best solution.

The separation, by partition chromatography, of mixtures of carboxylic acids has often been reported, but there is little literature on the separation of benzene-carboxylic acids by this method, although Turrizianni and Giovanni[2] have described such a separation of benzoic, phthalic, *iso*phthalic, and trimesic acid. The method now devised for the separation of benzene-carboxylic acids is similar to that described by Marvel and Rands[3] for other non-volatile acids.

Although Marvel and Rands[3] and others[4] have used water as stationary phase, some authors[2,5] buffered the column with mineral acid to obtain sufficiently sharp peaks. For

[1] Roy and Howard, *J. Amer. Chem. Soc.*, 1952, **74**, 3239.
[2] Turrizianni and Giovanni, *Ricerca sci.*, 1954, **24**, 2099.
[3] Marvel and Rands, *J. Amer. Chem. Soc.*, 1950, **72**, 2642.
[4] Baldwin, Loeblick, and Lawrence, *Analyt. Chem.*, 1954, **26**, 760; Roberts and Martin, *ibid.*, p. 815.
[5] Isherwood, *Biochem. J.*, 1946, **40**, 688; Donaldson, Tulane, and Marshall, *Analyt. Chem.*, 1952, **24**, 185; Bulen, Varner, and Burrell, *ibid.*, p. 187.

the separation of benzene-carboxylic acids, mineral acid (preferably 0·5N-sulphuric acid) is required as stationary phase when *n*-butanol–chloroform is used as mobile phase. The mixture to be separated is best added to the column in methanol–chloroform, as some of the mixture is carried through with the solvent front when it is added in *n*-butanol–chloroform.

Peaks are sharp and well separated, except that only partial separation of phthalic from *iso*phthalic acid takes place although peaks are sufficiently well separated for identification of both acids.

Peak effluent volumes are fairly constant and can be used for identification of the acids.

Recoveries of individual acids after separation (measured by the areas under the corresponding peaks) are close to 100% in most cases, with the exceptions of hemimellitic acid (95%), benzene-1 : 2 : 3 : 5-tetracarboxylic acid (95%), benzenepentacarboxylic acid (89%), and mellitic acid (91%). In these cases losses are reproducible so that satisfactory corrections can be applied.

Losses of acids during partition chromatography, owing to esterification, can be avoided by substituting *tert.*-butyl alcohol [6] or a ketone [7] for *n*-butanol in the eluting solvent. If losses of some benzene-carboxylic acids during chromatography are due to esterification, these losses might be avoided by using either of the above solvent mixtures, although separations might be less sharp with the ketone.

All the less common benzene-carboxylic acids used were prepared in the laboratory. In general these preparations involved oxidation of aromatic hydrocarbons, or suitable ketonic derivatives prepared from aromatic hydrocarbons by Friedel–Crafts reactions. Contrary to reports,[8] the oxidation of highly methylated benzene hydrocarbons, although slow, gave good yields (over 50%) of acids.

Some of the acids, *i.e.*, pyromellitic, benzenepentacarboxylic, and mellitic, were of considerably higher m. p. than previously reported.

In the preparation of benzene-1 : 2 : 3 : 5-tetracarboxylic acid by oxidation of 2 : 4 : 6-trimethylacetophenone, a good yield of 2-carboxyformyltrimesic acid was produced first. This was then oxidised, in poor yield, to the required product.

As part of an attempted preparation of benzene-1 : 2 : 3 : 4-tetracarboxylic acid [8] a dihydronaphthalene-1 : 4-dicarboxylic acid,[9] presumably pure, was dehydrogenated with bromine. Instead of the expected naphthalene-1 : 4-dicarboxylic acid, a brominated product was produced, oxidation of which gave a mixture of approximately equal quantities of phthalic, benzene-1 : 2 : 3 : 4-tetracarboxylic and benzene-1 : 2 : 3 : 5-tetracarboxylic acid, the tetra-acids being inseparable by crystallisation. The formation of benzene-1 : 2 : 3 : 5-tetracarboxylic acid is of significance, since it implies that the treatment of the reaction product from sodium and naphthalene with carbon dioxide yields a dihydronaphthalene-1 : 3-dicarboxylic acid in addition to the 1 : 2- and the 1 : 4-acid previously known to be formed.

Experimental

Chromatography.—Materials used. The "Pyrex"-glass tube (1·8 cm. diam.) was fitted with a tap and sintered-glass disc at the bottom. The height of the tube above the disc should be at least 40 cm.

Silica gel,[11] prepared for chromatography [11] (Messrs. Hopkin and Williams), was used.

Chloroform and *n*-butanol were of analytical quality. Solvent mixtures were prepared by shaking appropriate volumes of *n*-butanol and chloroform with a little distilled water and separating the organic layer.

[6] Resnick, Lee, and Powell, *Analyt. Chem.*, 1955, **27**, 928.
[7] Scott, *ibid.*, p. 367.
[8] Smith and Carlson, *J. Amer. Chem. Soc.*, 1939, **61**, 288.
[9] Walker and Scott, *ibid.*, 1938, **60**, 953.

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Procedure. Silica gel (20 g.) and 0·5N-sulphuric acid (10 ml.) are mixed and then slurried with chloroform (80 ml.). The column is packed, at atmospheric pressure, so that the rate of flow is about 3 ml./min.

Acid mixture (up to about 0·1 g.) is dissolved in methanol (0·4 ml.) and diluted with chloroform (0·6 ml.). The solution is added to the top of the column, from a capillary held just above the surface, and allowed to drain into the column. The procedure is repeated twice with washings from the flask, which consist successively of 10% methanol–chloroform (1 ml.) and chloroform (1 ml.).

Chloroform (50 ml.) is added to the column and elution commenced, the eluant being collected in 10-ml. fractions. More solvent is added portionwise (each 50 ml.) before the last 10 ml. of the preceding solvent has drained into the column. The complete range of solvents is chloroform (50 ml.), followed by the following *n*-butanol–chloroform mixtures: 2·5%, 150 ml.; 10%, 100 ml.; 12·5%, 100 ml.; 17·5%, 100 ml.; 25%, 100 ml.; 30%, 100 ml.; 40%, 100 ml.; 50%, 100 ml.; 70%, 200 ml.

With concentrations of alcohol up to about 40%, a flow rate of 2—3 ml./min. can be maintained at atmospheric pressure. At higher concentrations it is necessary to apply slight positive pressure to maintain the rate.

The acid in each fraction is estimated, after addition of water (50 ml.) and a little phenolphthalein, by titration with 0·02N-sodium hydroxide.

Values (ml.), each being the mean of several determinations of peak effluent volumes are as follows: benzoic acid, 20, *iso*phthalic acid, 83, phthalic acid, 108, trimesic acid, 225, trimellitic acid, 254, hemimellitic acid, 359, benzene-1 : 2 : 3 : 5-tetracarboxylic acid, 452, pyromellitic acid, 508, benzene-1 : 2 : 3 : 4-tetracarboxylic acid, 631, benzenepentacarboxylic acid, 808, and mellitic acid, 1040.

Peak effluent volumes were also determined for the two keto-acids, 2-carboxyformyl*iso*phthalic acid, 252, and 2-carboxyformyltrimesic acid, 357. These acids were isolated during attempted preparations of hemimellitic and benzene-1 : 2 : 3 : 5-tetracarboxylic acids, respectively.

Preparation and Isolation of the Acids.—Benzoic and the phthalic acids were obtained commercially. All other acids were prepared in the laboratory.

The hydrocarbon or ketone was oxidised by (generally prolonged) boiling with an excess of aqueous alkaline potassium permanganate. Except for hemimellitic acid, which was purified *via* the barium salt, all the acids were recovered by the following procedure. The excess of permanganate was destroyed and the solution filtered. After acidification with hydrochloric acid the filtrate was evaporated to dryness (water-bath) and the solid residue was extracted with ether, in a Soxhlet apparatus, until all the organic material was removed. The ethereal extract was evaporated to dryness giving the benzene-carboxylic acid which was recrystallised.

Trimesic acid. This acid was obtained from mesitylene (69%; m. p. not determined) and crystallised from 50% aqueous ethanol (Found: C, 51·5; H, 2·5; equiv., 71·7. Calc. for $C_9H_6O_6$: C, 51·4; H, 2·9%; equiv., 70·0).

Trimellitic acid. Oxidation of 2 : 4-dimethylacetophenone gave the acid, m. p. 221—222° (from dilute hydrochloric acid) (Found: C, 50·9; H, 3·1%; equiv., 71·0).

Hemimellitic acid. Oxidation of acenaphthene gave crude 2-carboxyformyl*iso*phthalic acid, which was converted into the *trimethyl ester* (m. p. 144—145°; from ethanol) (Found: C, 55·4; H, 4·2. $C_{13}H_{12}O_7$ requires C, 55·7; H, 4·3%). Subsequent hydrolysis gave the pure *acid*, m. p. 230—231° (Found: C, 45·6; H, 3·7%; equiv., 87·4. $C_{10}H_6O_7,1\frac{1}{2}H_2O$ requires C, 45·3; H, 3·4%; equiv., 87·3).

Hemimellitic acid (40%; m. p. 195—197°) was prepared from naphthalic anhydride, after Graebe and Leonhardt's method [10] (Found: C, 44·3; H, 4·3%; equiv., 81·9. Calc. for $C_9H_6O_6,2H_2O$: C, 43·9; H, 4·1%; equiv., 82·0).

Pyromellitic acid. Oxidation, for 72 hr., of 1 : 2 : 4 : 5-tetramethylbenzene gave pyromellitic acid (61%), m. p. 285—287° (from water) (Found: C, 41·2; H, 3·5%; equiv., 72·0. Calc. for $C_{10}H_6O_8,2H_2O$: C, 41·4; H, 3·5%; equiv., 72·5).

Benzene-1 : 2 : 3 : 5-tetracarboxylic acid. Oxidation of 2 : 4 : 6-trimethylacetophenone and crystallisation from dilute hydrochloric acid (1 : 1) gave *2-carboxyformyltrimesic acid* (91%), m. p. 252° (Found: C, 47·0; H, 2·2%; equiv., 71·3. $C_{11}H_6O_9$ requires C, 46·8; H, 2·1%;

[10] Graebe and Leonhardt, *Annalen*, 1896, **290**, 218.
[11] Fieser and Peters, *J. Amer. Chem. Soc.*, 1932, **54**, 4347.

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equiv., 70·5). The *tetramethyl ester* had m. p. 168—168·5° after crystallisation from ethanol (Found: C, 53·2; H, 4·2. $C_{15}H_{14}O_9$ requires C, 53·3; H, 4·1%).

Prolonged oxidation of the keto-acid gave benzene-1 : 2 : 3 : 5-tetracarboxylic acid (26%), m. p. 246—247° (from dilute hydrochloric acid; 1 : 1) (Found: C, 47·2; H, 2·4%; equiv., 62·7. Calc. for $C_{10}H_6O_8$: C, 47·3; H, 2·4%; equiv., 63·5).

Benzene-1 : 2 : 3 : 4-tetracarboxylic acid. β-(3-Acenaphthoyl)propionic acid, m. p. 210·5—212°, was prepared by Fieser and Peters's method.[11] On oxidation, this acid gave benzene-1 : 2 : 3 : 4-tetracarboxylic acid (63%), m. p. 236·5—238° (from dilute hydrochloric acid; 1 : 1) (Found: C, 47·9; H, 2·5%; equiv., 63·8).

Benzenepentacarboxylic acid. The oxidation, for 40 hr., of pentamethylbenzene gave the penta-acid (59%), m. p. 236·5—237° (from dilute hydrochloric acid) (Found: C, 38·5; H, 3·2%; equiv., 68·7. Calc. for $C_{11}H_6O_{10},2\frac{1}{2}H_2O$: C, 38·5; H, 3·2%; equiv., 68·6).

Mellitic acid. 72 Hours' oxidation of hexamethylbenzene gave mellitic acid (99%), m. p. 307° (from hydrochloric acid; 1 : 1) (Found: C, 41·6; H, 1·6%; equiv., 57·2. Calc. for $C_{12}H_6O_{12}$: C, 42·1; H, 1·8%; equiv., 57·0).

This work is published by permission of the National Coal Board. The author thanks Dr. J. Barrott and Miss M. A. Purslow for help with the later stages of the work.

NATIONAL COAL BOARD, COAL SURVEY LABORATORY,
14, ENDCLIFFE AVENUE, SHEFFIELD, 10. [*Received, August 15th*, 1956.]

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234. *Some Reactions of* cyclo*Propane and a Comparison with the Lower Olefins. Part III.* The Friedel–Crafts Reaction.*

By C. F. H. TIPPER and D. A. WALKER.

The kinetics of the reaction of *cyclo*propane and of propene with benzene in the presence of aluminium chloride in homogeneous solution have been investigated at *ca.* 25°. Some comparative results were obtained with toluene and chlorobenzene. Traces of water and/or hydrogen chloride were necessary as co-catalysts. With *cyclo*propane the initial rate depended only on the catalyst concentration at " high " gas pressures and concentrations of aromatic compound, while at " low " concentrations the rate also varied with the pressure of gas and the nature and concentration of the aromatic compound. With propene the rate actually fell as the benzene concentration was increased above a certain value.

The nature of the effective catalyst and the mechanism of the reaction are discussed and a scheme is put forward to explain the kinetic results. It is suggested that several complexes involving the various reagents were present in the solution.

OLEFINS readily combine with many aromatic compounds in the presence of Friedel–Crafts catalysts, and Schmerling [1] showed that, when *cyclo*propane was passed into a solution of aluminium chloride and benzene in nitromethane at room temperature, *n*-propylbenzene was formed quantitatively. With propene the product was *iso*propylbenzene. The kinetics of these reactions have been investigated and the results are now presented.

EXPERIMENTAL

The rate of uptake of *cyclo*propane or propene was followed by means of the conventional constant-pressure apparatus used previously. It was found that the rate did not increase as the speed of shaking of the reaction flask was increased, provided this was above 250 times per minute. The standard shaking speed was thus fixed at about 400 times per minute. The flask was cleaned before an experiment by washing it with alcohol, drying it thoroughly and flaming it.

* Part II, *J.*, 1955, 2045.

[1] Schmerling, *Ind. Eng. Chem.*, 1948, **40**, 2072.

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*cyclo*Propane and propene from cylinders were purified as described,[2] and dried [$Mg(ClO_4)_2$]. Ethylene from a cylinder was passed through 82·5% sulphuric acid and a trap at −78°, and dried. Chlorobenzene, and " AnalaR " benzene, nitrobenzene, and diethyl ether were dried thoroughly, and fractionally distilled in a stream of dry nitrogen. The toluene was shaken several times with concentrated sulphuric acid, washed, and distilled from sodium. The nitromethane was purified as recommended by Thompson, Coleman, and Helm.[3]

Hydrogen chloride was passed through concentrated sulphuric acid and then over heated aluminium turnings (" specially pure," 99·9%). The aluminium chloride formed was condensed in a receiver with a side tube. After a suitable amount had been collected, dry nitrogen was passed for several hours to remove excess of hydrogen chloride. The receiver was then cooled in ice and the purified nitromethane or nitrobenzene run in with nitrogen still passing. The solution was colourless but slowly deteriorated, becoming brown, and thus a fresh solution was prepared every few days. Any appreciable quantity of hydrogen chloride or water gave a yellow tint or a white cloudiness respectively, and such samples were discarded. The reactants were protected from atmospheric moisture during storage, measurement of the appropriate volumes, and transfer to the reaction flask. If required, water was added to the reaction mixture from a microburette, and hydrogen chloride by shaking a bulk sample of the aluminium chloride solution with the dried gas.

Two very dry solutions of aluminium chloride and benzene in nitromethane were prepared in a vacuum system by a method similar to that used by Fairbrother, Scott, and Prophet.[4] The solutions were stored in an atmosphere of dry carbon dioxide in sealed tubes until required.

Results

The following systems were studied: I, aluminium chloride–nitromethane–benzene–*cyclo*propane (with and without added water and hydrogen chloride); II, aluminium chloride–nitromethane–benzene–propene; III, aluminium chloride–nitrobenzene–benzene–*cyclo*propane; IV, aluminium chloride–nitromethane–diethyl ether–benzene–*cyclo*propane; V, aluminium chloride–nitromethane–toluene–*cyclo*propane; and VI, aluminium chloride–nitromethane–chlorobenzene–*cyclo*propane. The solubilities of *cyclo*propane in nitromethane, benzene, and 0·10M-aluminium chloride in nitromethane are roughly 0·16, 0·46, and 0·24 mole/l. respectively at 25° and atmospheric pressure. The solubility of propene is also greater in benzene than in nitromethane.

Removal of traces of water and hydrogen chloride in the vacuum apparatus gave solutions which did not react at an appreciable rate with *cyclo*propane. With reactants prepared in the normal manner, however, reaction took place with systems I to VI. After a very rapid absorption, due to physical solution of the gas, the rate of uptake (" initial rate ") remained constant for some time and then decreased gradually. Rates were reproducible to within 5—10% and were almost certainly equal to the rates of reaction. The effect of conditions on the initial rate was studied.

The initial rate of reaction with propene was several times greater than with *cyclo*propane under the same conditions (systems II and I), but ethylene was absorbed only very slowly. Addition of roughly 0·1 mole/l. of hydrogen chloride to system I increased the initial rate by about 1·5—2·5 times, depending on the benzene concentration. Fig. 1 shows the effect of adding water to the same system. Very small amounts increased the initial rate to 10 times the value with reactants purified in the normal manner, but further additions reduced the rate again although not to zero, and precipitation occurred. The results are consistent with the fact that there was no reaction with completely dry reagents.

The initial rate increased rapidly with increasing aluminium chloride concentration (Fig. 2). The plots are slightly curved but the order with respect to catalyst concentration is approximately unity for both *cyclo*propane and propene. Variation of the gas pressure had little effect on the initial rate, whether the solvent was nitromethane or nitrobenzene and the aromatic reactant benzene or toluene (Fig. 3). In the presence of hydrogen chloride however, the rate with system I decreased somewhat with increasing *cyclo*propane pressure (650—900 mm.). The results

[2] Lawrence and Tipper, *J.*, 1955, 713.
[3] Thompson, Coleman, and Helm, *J. Amer. Chem. Soc.*, 1954, **76**, 3445.
[4] Fairbrother, Scott, and Prophet, *J.*, 1956, 1164.

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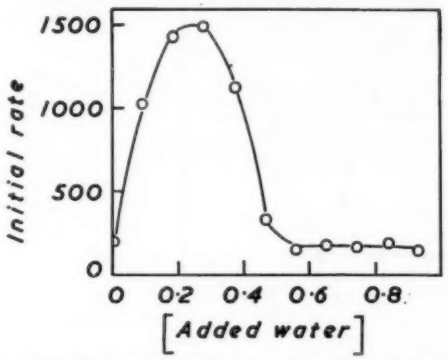
are rather scattered due to the difficulty of measuring the high rates accurately. The plots must pass through the origin, and therefore at low pressures the rate must depend on the concentration of *cyclo*propane or propene in the solution. There is some experimental evidence of this (Fig. 3, curve *b*; see also Fig. 5).

With system I and constant concentrations of aluminium chloride and *cyclo*propane the initial rate increased at first with increasing benzene concentration, and then became constant

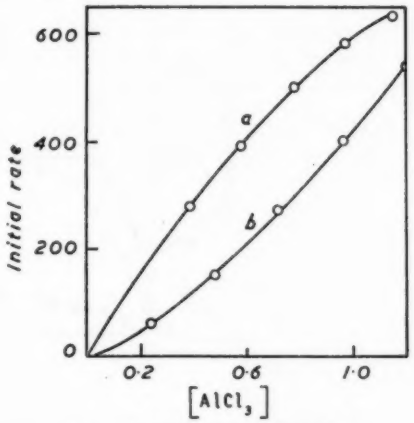
In all Figures, concentrations are in moles/l.

FIG. 1. *Effect of added water on the initial rate (ml. at N.T.P./l./min.) of uptake of* cyclo*propane (pressure 760 mm.) at 24·7° C. Solvent, nitromethane*; $[AlCl_3]$, 0·32; $[C_6H_6]$, 1·82.



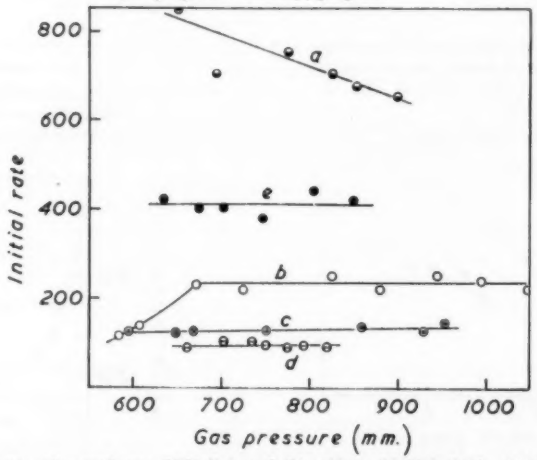
At concentrations greater than that of the experimental point corresponding to the highest rate there was precipitation.

FIG. 2. *Effect of concentration of aluminium chloride on the initial rate of uptake of gas (pressure, 760 mm.) at 24·1° C. Solvent, nitromethane.*



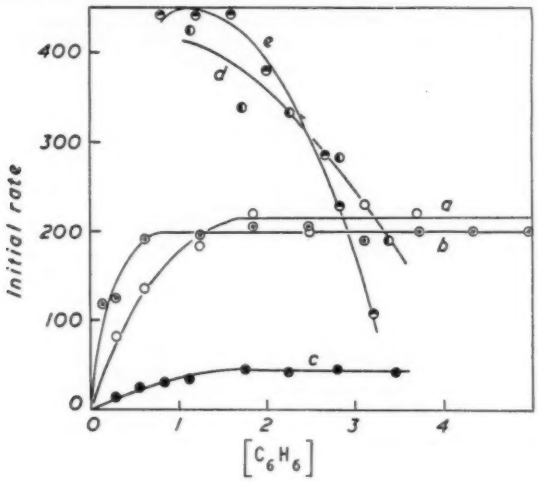
(*a*) cyclo*Propane*: $[C_6H_6]$, 4·35.
(*b*) Propene: $[C_6H_6]$, 5·45.

FIG. 3. *Effect of pressure on the initial rate of uptake of gas at 24·7° C. Gas: curves (a)—(d),* cyclo*propane; curve (e) propene.*



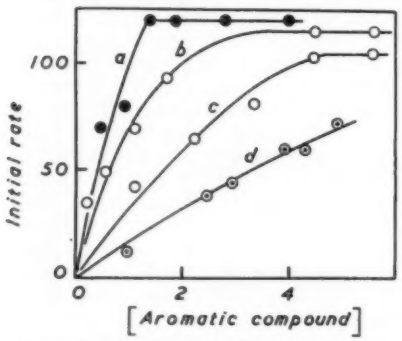
(*a*) *Solvent, nitromethane*; HCl (0·1 *mole/l.*) *added*; $[C_6H_6]$, 2·73; $[AlCl_3]$, 0·48.
(*b*) *Solvent, nitromethane*; $[C_6H_6]$, 2·48; $[AlCl_3]$, *not determined.*
(*c*) *Solvent, nitromethane*; $[C_6H_5Me]$, 1·60; $[AlCl_3]$, 0·088.
(*d*) *Solvent, nitrobenzene*; $[C_6H_6]$, 2·73; $[AlCl_3]$, 0·187.
(*e*) *Solvent, nitromethane*; $[C_6H_6]$, 4·35; $[AlCl_3]$, 0·17.

FIG. 4. *Effect of benzene concentration on the initial rate of uptake of gas (pressure 760 mm) at 24·7° c. Gas: curves (a)—(d), cyclopropane; (e) propene.*



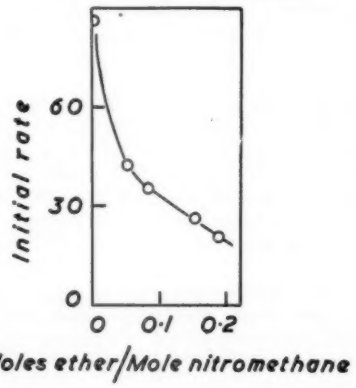
(*a*) *Solvent, nitromethane*; [$AlCl_3$], *not determined.*
(*b*) *Solvent, nitromethane*; *water* (0·06 *mole/l.*) *added*; [$AlCl_3$], 0·074.
(*c*) *Solvent, nitrobenzene*; [$AlCl_3$], 0·292.
(*d*) *Solvent, nitromethane*; HCl (0·1 *mole/l.*) *added*; [$AlCl_3$], 0·48; *ordinate and abscissa* × 2.
(*e*) *Solvent, nitromethane*; [$AlCl_3$], 0·12; *ordinate and abscissa* × 2.

FIG. 5. *Effect of concentration of benzene, toluene, and chlorobenzene on the initial rate of uptake of* cyclo*propane at 24·7° c. Solvent, nitromethane.*



(*a*) *Toluene*; [$AlCl_3$], 0·067; *gas pressure,* 760 *mm.*
(*b*) *Benzene*; [$AlCl_3$], 0·067; *gas pressure,* 885 *mm.*
(*c*) *as* (*b*); *gas pressure,* 613 *mm.*
(*d*) *Chlorobenzene*, [$AlCl_3$], 0·130; *gas pressure,* 760 *mm.*

FIG. 6. *Effect of replacement of nitromethane by diethyl ether on the initial rate of uptake of* cyclo*propane (pressure,* 760 *mm.) at* 24·1° c. [$AlCl_3$], 0·057 [C_6H_6], 0·91.



(Fig. 4, curve *a*). With a very small addition of water the rate became independent of benzene concentration at a much lower value of this concentration (curve *b*). Replacement of the nitromethane by nitrobenzene reduced the rates considerably, but the form of the dependence on benzene concentration was the same (curve *c*). With addition of hydrogen chloride or with propene however, the initial rate fell rapidly as the benzene concentration was increased above a relatively small value (curves *d* and *e*). With added hydrogen chloride about 60% of the fall in rate is accounted for by the increase in *cyclo*propane concentration with increase in benzene concentration.

Fig. 5 shows the effect on the initial rate of uptake of *cyclo*propane of the concentrations of benzene, toluene, and chlorobenzene, the same catalyst solution being used with the first two

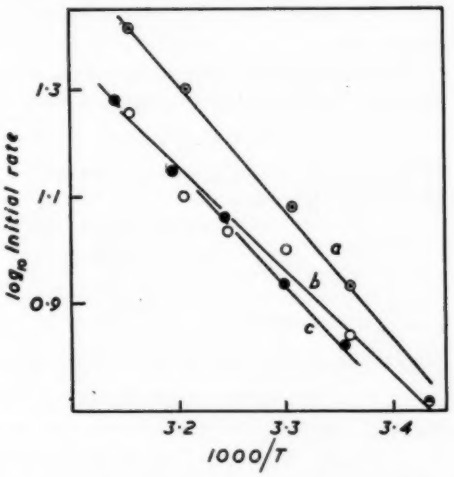


FIG. 7. *Effect of temperature on the initial rate of uptake of* cyclo*propane* (*pressure*, 760 *mm.*).

(*a*) *Solvent, nitromethane*; [$AlCl_3$], 0·061; [C_6H_5Me], 4·0.
(*b*) *Solvent, nitromethane*; [$AlCl_3$], 0·061; [C_6H_6], 5·5.
(*c*) *Solvent, nitrobenzene*; [$AlCl_3$], 0·098; [C_6H_6], 4·05.

compounds. As the concentration of benzene or toluene was increased the rate increased to a constant value which was nearly the same for the two substances. However, the actual concentration at which the rate became independent of the amount of aromatic increased in the order: toluene, benzene ("high" *cyclo*propane pressure), benzene ("low" *cyclo*propane pressure). With chlorobenzene, the rate continued to increase with increasing concentration within the range used.

Replacement of increasing amounts of nitromethane by ether led to a rapid decrease in the initial reaction rate (system IV) (Fig. 6).

The effect of temperature on the initial rate of *cyclo*propane uptake was investigated with systems I, III, and V, under conditions where the rate was independent of benzene or toluene concentration (Fig. 7). The overall activation energies are 8·9, 10·2, and 10·9 kcal./mole with I, III, and V, respectively.

DISCUSSION

The fact that a co-catalyst was required for the addition of *cyclo*propane to benzene agrees with observations of other workers on many types of Friedel–Crafts reaction.[5] Traces of water and hydrogen chloride were undoubtedly present in the reactants purified in the normal manner. However, consideration of the effective catalyst will be deferred until after a scheme has been proposed to explain the observed kinetics. In this scheme the active form of the aluminium chloride will be denoted as "cat."

The theory of Friedel–Crafts reactions has been discussed recently by Nelson and Brown.[6] It is generally considered that in an alkylation the alkylating agent first combines with the catalyst and then the complex reacts with the aromatic compound. In this

[5] Brooks, Boord, Kurtz, and Schmerling (Editors), "The Chemistry of Petroleum Hydrocarbons," Reinhold Publishing Corporation, 1955, Vol. 3, pp. 185, 511.
[6] Nelson and Brown, ref. 5, p. 510.

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work the higher solubility of *cyclo*propane in a solution of aluminium chloride in nitromethane than in the solvent alone suggests the existence of a catalyst–C_3H_6 complex. Also Schmerling [1] has obtained a solid 1 : 1 complex of aluminium chloride and nitromethane. Several complexes have to be postulated in the reaction scheme given below, and these have been chosen with these considerations in mind.

$$\underset{\text{(complex 1)}}{\text{cat,RNO}_2} + C_3H_6 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \underset{\text{(complex 2)}}{\text{cat,RNO}_2\cdot C_3H_6} \underset{k_4}{\overset{k_3}{\rightleftharpoons}} \underset{\text{(complex 3)}}{\text{cat}\cdot C_3H_6} + \text{RNO}_2$$

$$\text{RNO}_2 + \text{cat,}C_3H_6 + C_6H_5X \xrightarrow{k_5} X\cdot C_6H_4\cdot C_3H_7 + \text{cat,RNO}_2$$

(R is either Me or Ph; X is H, Me, or Cl)

It is assumed that all the catalyst was in the form of complexes 1, 2, and 3, and that the presence of a solvent molecule was necessary in reaction 5 to combine with the catalyst released.

$$\text{Rate of uptake} = -\text{d}[C_3H_6]/\text{d}t = k_1[1][C_3H_6] - k_2[2]$$

It being assumed that in a very short time stationary concentrations of complexes 2 and 3 were attained, then

$$k_1[1][C_3H_6] + k_4[3][\text{RNO}_2] = k_2[2] + k_3[2]$$

and $$k_3[2] = k_4[3][\text{RNO}_2] + k_5[3][\text{RNO}_2][C_6H_5X]$$

$\therefore$ $$-\text{d}[C_3H_6]/\text{d}t = k_5[3][\text{RNO}_2][C_6H_5X]$$

Also $$[1] + [2] + [3] = [\text{cat}]$$

Thus solving for the stationary concentration of complex 3 gives

$$[3] = k_1k_3[\text{cat}][C_3H_6]/\{k_1x + k_5x[C_6H_5X] + k_1k_3[C_3H_6] - k_3k_4\}$$

where $x = k_1[C_3H_6] + k_2 + k_3$

$\therefore$ $$-\text{d}[C_3H_6]/\text{d}t = k_1k_3k_5[\text{cat}][C_3H_6][C_6H_5X]/$$
$$\{k_2k_4 + (k_1k_4 + k_3k_5)[C_3H_6] + k_5(k_2 + k_3)[C_6H_5X] + k_1k_5[C_3H_6][C_6H_5X]\} \quad . \quad (a)$$

This theoretical relation agrees with the experimental dependence of the rate on aluminium chloride concentration, on the assumption that this was proportional to the actual catalyst concentration during the appropriate sets of experiments.

At high concentrations of both *cyclo*propane and the aromatic compound the expression reduces to

$$-\text{d}[C_3H_6]/\text{d}t = k_3[\text{cat}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (b)$$

the rate being independent of the concentration of both organic reagents, and actually independent of the aromatic compound itself with the same solvent and catalyst solution. This was found experimentally with benzene and toluene. Probably with chlorobenzene the rate would have become independent of the concentration if it had been possible to make this large enough. Equation (*a*) implies a dependence of the rate on the concentration at low concentrations of aromatic compound, as found.

The lower rates obtained with nitrobenzene, compared to those with nitromethane as solvent, suggest that k_3 was smaller with the former and thus that complex 2 was more stable with nitrobenzene than with nitromethane. According to equation (*b*), the variation of the initial rates of uptake with temperature should give the activation energies for the decomposition of complex 2 to complex 3, since the concentrations of aromatic substance and *cyclo*propane were "high." It might be expected therefore that the activation energy for the reaction of *cyclo*propane and benzene in nitromethane solution would be less than in nitrobenzene solution, as found experimentally. However, the activation energy for the reaction with toluene was somewhat greater than with benzene, instead of being approximately the same. This was probably due to the appreciably different environment of complex 2, since a considerable fraction of the solution consisted of molecules of

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benzene or toluene ($N_{C_6H_5X} \sim 0{\cdot}3$). The marked effect of small amounts of ether on the rate can have been due only in part to a reduction in the dielectric constant of the solvent, and it is probable that the aluminium chloride and ether tended to form an inactive complex, possibly $AlCl_3,Et_2O$.[7]

Equation (*a*) agrees with the experimental findings that the rate became dependent on the gas pressure at " low " pressures, and that the higher the pressure of *cyclo*propane the lower the benzene concentration at which the rate became independent of the concentration.

It can be seen from Fig. 5 that k_5 increased in the order $C_6H_5Cl < C_6H_6 < C_6H_5{\cdot}CH_3$. This implies that complex 3 was an electrophilic reagent, and suggests a carbonium-ion mechanism for reaction 5, in agreement with other work.[8]

With propene the decrease in rate with increasing benzene concentration at the higher concentrations may be explained by postulating that the equilibrium

$$\underset{\text{(complex 2)}}{\text{cat,}CH_3{\cdot}NO_2\text{,propene}} + C_6H_6 \rightleftharpoons \text{cat,}CH_3{\cdot}NO_2,C_6H_6 + \text{propene}$$

occurred in addition to the other reactions. With system 1 in the presence of added hydrogen chloride the small retarding effect of *cyclo*propane at " high " pressures must presumably have been due to formation of an inactive *cyclo*propane–catalyst complex.

The scheme suggested is of course not the only one which will explain the kinetic results, but it does appear to be the simplest which does not contradict the other evidence concerning the mechanism of Friedel–Crafts reactions. Brown *et al.*[9] have investigated the alkylation of benzene and toluene by alkyl bromides in the presence of aluminium bromide. In particular they found that *iso*propylation was too fast to measure even in 1 : 2 : 4-trichlorobenzene. Their reaction scheme is very similar to that suggested here. The differences between the rates and kinetics with the two systems is probably at least partly due to the highly polar nature of nitromethane and nitrobenzene, which caused complex 2 to be relatively stable.

The nature of the actual catalyst in a Friedel–Crafts alkylation is by no means clear. Many workers have considered that in the presence of hydrogen chloride (which could be produced by the hydrolysis of some aluminium chloride; cf. Bercaw and Garrett [10]), $HAlCl_4$ is formed and combines with the olefin, giving $C_nH_{2n+1}{}^+AlCl_4{}^-$. This would be complex 3 in our scheme. Recent work [11] has shown that the $AlCl_4{}^-$ ion can only be formed from aluminium chloride and hydrogen chloride if there is a proton acceptor present, and results by Fairbrother and Frith,[12] who studied the effect of water on aluminium bromide, have cast doubt on the possibility of rapid hydrolysis of aluminium chloride by traces of water. They present strong evidence for the complex $AlBr_3,H_2O$, and it is noteworthy that in this work the maximum in the curve of rate against concentration of added water corresponds to approximately one mole of water per mole of alumium chloride (the curve being extrapolated to zero rate). The reduction in the rate with larger additions of water was probably due to precipitation of some or all of the aluminium. This precipitate presumably could catalyse the reaction to some extent since the rate did not fall to zero. However, the effect of added hydrogen chloride can hardly be attributed completely to traces of water which escaped the drying process so that it seems likely that the active catalyst was in effect the proton, the negative ion being $AlCl_4{}^-$ and $AlCl_3{\cdot}OH^-$. Addition of relatively small amounts of water or hydrogen chloride increased the number of protons made available, though the former was the much more effective co-catalyst. It is useless

[7] Thomas, " Anhydrous Aluminium Chloride in Organic Chemistry," Reinhold Publishing Corporation, 1941.
[8] Nelson and Brown, ref. 5, p. 159.
[9] Brown and Jungk, *J. Amer. Chem. Soc.*, 1956, **78**, 2182; Jungk, Smoot, and Brown, *ibid.*, p. 2185.
[10] Bercaw and Garrett, *J. Amer. Chem. Soc.*, 1956, **78**, 1841.
[11] Brown and Pearsall, *J. Amer. Chem. Soc.*, 1951, **73**, 4681.
[12] Fairbrother and Frith, *J.*, 1953, 2975.

to speculate on the structures of complexes 1 and 2 but it is probable that the *cyclo*propane ring or the double bond were broken as *n*- or *iso*-$C_3H_7^+$ ions, respectively, were formed.

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DEPARTMENT OF INORGANIC AND PHYSICAL CHEMISTRY,
UNIVERSITY OF LIVERPOOL. [*Received, September 20th,* 1956.]

235. *Mechanism of Substitution at a Saturated Carbon Atom. Part LIII.* Conductances of Some Quaternary Ammonium Salts in Benzene, as a Preliminary to the Study of Unimolecular Nucleophilic Substitution in that Solvent.*

By E. D. HUGHES, C. K. INGOLD, S. PATAI, and Y. POCKER.

A revised plan for investigation of unimolecular nucleophilic substitution in polar and non-polar aprotic media is indicated. In preparation for a kinetic study in the non-polar medium, benzene, in which salts would be used as reagents, sometimes with other salts present to change the reaction rate, or to divert reaction, a study is undertaken of the conductance in benzene of the salts of interest, both singly and as mixtures, for the purpose of elucidating the involved electrolytic equilibria. The salts employed were tetra-*n*-butylammonium chloride, azide, nitrate, and perchlorate, alone and in pairs. The dissociation constants and concentrations are derived for all species up to triple ions, including the unsymmetrical triple ions given by the mixtures. A less quantitative study was made of mixtures of single salts with hydrogen chloride, and it is shown that the anions $(ClHCl)^-$ and $(ClHNO_3)^-$ are stable in benzene. Thus the conditions have been found in which interpretable kinetics can be expected in reactions in benzene involving salts, and a control has been provided on the interpretation of kinetic results.

(1) *Introduction to a Group of Papers.*—The nature of the unimolecular mechanism of nucleophilic substitution and elimination has long been a subject of controversy, because the first investigations of it (1933—1940) related to solvolytic substitution, for which the most elementary kinetic criterion of mechanism is unavailable. The circumstance that kinetically unimolecular non-solvolytic substitutions, as by azide ions acting on benzhydryl halides (diphenylmethyl halides) in aqueous acetone, could be arranged to accompany unimolecular solvolysis, seems to have made little impression on discussions of this mechanism. Therefore considerable interest attaches to unimolecular substitutions in conditions in which solvolysis is excluded by the use of aprotic media. The first experiments of this kind were made in solvent sulphur dioxide;[1] but it was subsequently decided that progress would be faster with a more manageable polar solvent, such as nitromethane, and a series of kinetic studies in this medium was commenced.[2] At that stage our idea was to investigate this solvent thoroughly, and then to use the knowledge gained in studies with successively less polar solvents, ending with the non-polar solvent, benzene. However, so many difficult questions have been raised by others on the basis of their kinetic experiments in benzene, that we have now decided to shorten this programme by conducting investigations in nitromethane and in benzene concurrently, and, giving up the progressive method, to try to establish the main phenomena at the two ends of the aprotic solvent series independently, leaving to the future the task of interpolating between them.

The following four papers present our first experimental kinetic studies of nucleophilic substitution in benzene, and to them the present paper is introductory. We must explain why its mood is predominantly electrochemical.

* Part LII, *J.*, 1956, 855.

[1] Bateman, Hughes, and Ingold, *J.*, 1940, 1011, 1017; Bird, Hughes, and Ingold, *J.*, 1954, 634; Bunton, Greenstreet, Hughes, and Ingold, *J.*, 1954, 642, 647.

[2] Gelles, Hughes, and Ingold, *J.*, 1954, 2918; de la Mare, Hughes, Ingold, and Pocker, *J.*, 1954, 2930.

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(2) *Purpose of the Present Paper.*—When facing the problem of what happens to a reaction, normally depending on ions, when it is transferred to a hydrocarbon solvent, the first thing to be clear about is the condition of undoubted ions in such a solvent. We know already that they will exist largely as ion-pairs, but that there may be present also a certain concentration of simple ions, as well as of more complex ionic aggregates.

We picture the problem of these nucleophilic substitutions in benzene as one to be approached in two successive stages. The first, and simpler, is that of substitution by reagent anions, particularly monatomic or symmetrical anions, such as chloride or azide, and this involves the use of salts. In problems of mechanism, illumination often follows from the kinetic effect of salts, such as perchlorates, which do not stoicheiometrically participate in reaction; and also from the forms of competition shown by simultaneous reagents which both participate. We therefore felt it necessary to familiarise ourselves with the electrochemistry of the principal salts which were to be used in the kinetic work, and to study them, not only alone, but also as mixtures.

The second, and more complicated, part of the mechanistic problem is that which concerns nucleophilic substitution with neutral dipolar molecules, such as alcohols or amines, as substituting agents. Even here, a knowledge of the electrochemistry of salts in the benzene medium must help, because it will necessarily include a study of ion-pairs. Such saline dipoles can be considered as a highly simplified model for molecular dipoles, and hence, if we can follow the associating properties of ion-pairs, and distinguish their function in reaction from those of other saline species, we shall have a reasonable basis on which to consider the behaviour of molecular reagents.

(3) *Ion–Ion and Ion–Dipole Interaction in Benzene.*—The mass law of chemical kinetics depends on the chance encounters of particles, which, for nearly the whole of their lives, are out of each other's force range, *i.e.*, at such separations that their mutual potential energy is negligible compared with their thermal kinetic energies. It is not altogether easy so to arrange kinetic experiments involving ions that this condition is fulfilled in a solvent, such as benzene, in which electrostatic forces extend over great distances. Two ions of unit charge in benzene will have a mutual electrostatic energy equal to the mean kinetic energy of either along a line, at a separation of about 500 Å. A cubic lattice of univalent ions with this spacing would correspond to a salt concentration of about 10^{-5}M. From well below this concentration to a long way above it, most of the ions must fall into pairs or other groups of shorter force range, leaving free ions only in much smaller concentration. Bjerrum[3] has defined an ion-pair as two counter-ions at any separation less than the statistically least prevalent one, down to contact. In solvents of higher dielectric constant an ion-pair can only be quite a compact assembly, but for univalent ions in benzene the maximum length of a pair is about 120 Å, though shorter pairs are much more prevalent.

These ideas have been extended by Fuoss and Kraus,[4] who have shown that in solvents of sufficiently low dielectric constants, simple ions will associate with pairs to form triple ions, which they analogously define as having an energy less than that of a most stable pair with a simple ion at the statistically least prevalent collinear distance from its attracting pole. In some solvents triple ions can only be close assemblies, but in those made from univalent ions in benzene, the maximum separation of unlike charges may amount to 40 Å, though most triple ions will be considerably more compact. Since they carry a net charge, triple ions, like simple ions, can appear only in very low concentration in benzene. The same authors have extended the theory to the next stage of association, in which the net charge is lost again in the formation of coupled pairs, or quadrupoles. At suitable salt concentrations, in a solvent such as benzene, quadrupoles can arise in appreciable proportions.

Fuoss and Kraus, whose methods we have followed, showed how to calculate, from the

[3] Bjerrum, *Kgl. danske Vidensk. Selskab, Mat.-fys. Medd.*, 1926, **7**, No. 9.
[4] Fuoss and Kraus, *J. Amer. Chem. Soc.*, 1933, **55**, 2387, 3614; 1935, **57**, 1.

curve of equivalent conductance, Λ, *versus* the salt concentration, c, an equilibrium constant, K_2, for the dissociation of pairs to simple ions,

$$M^+X^- \rightleftharpoons M^+ + X^- \qquad K_2 = [M^+][X^-]/[M^+X^-]$$

and also an average equilibrium constant, K_3, averaged by an assumed equality, for the dissociation of triple cations and anions, each to an ion-pair plus a simple ion:

$$\left.\begin{array}{l} M^+X^-M^+ \rightleftharpoons M^+X^- + M^+ \\ X^-M^+X^- \rightleftharpoons X^- + M^+X^- \end{array}\right\} \qquad K_3 = \frac{[M^+X^-][M^+]}{[M^+X^-M^+]} = \frac{[X^-][M^+X^-]}{[X^-M^+X^-]}$$

In solvents of low dielectric constant these Λ–c curves go through a minimum, $\Lambda_{min.}$, at some salt concentration, $c_{min.}$, usually between 10^{-5} and 10^{-3}M. At very low concentration, when the curve has a negative gradient, simple ions carry most of the current, and at the lowest concentrations, when they are almost the only carriers, Ostwald's law for weak electrolytes is obeyed. Immediately on the high-concentration side of the minimum, the main carriers are the triple ions. Further on, the gradient of the now rising conductance curve slackens, as quadrupoles begin to be formed, and further on still it steepens again, often somewhat irregularly, as higher charged complexes are produced. So long as the proportions of all species other than ion-pairs are small, the equation which takes account of all species up to quadrupoles is:

$$\Lambda = Ac^{\frac{1}{2}} + Bc^{\frac{1}{2}} - Cc$$

Thus if we plot $\Lambda\sqrt{c}$ against c, a line is obtained, the initial straight part of which gives A and B, as intercept and slope, respectively, which are related to K_2 and K_3; whilst, when the curve begins to reduce its positive gradient, we know that quadrupoles are beginning to be formed. The equations [5] giving K_2 and K_3 are:

$$c_{min.} = A/B \qquad \Lambda_{min.} = 2\sqrt{AB}$$

$$K_2 = c_{min.}(\Lambda_{min.}/2\Lambda_1^\circ)^2 \qquad K_3 = c_{min.}(\Lambda_3^\circ/\Lambda_1^\circ)$$

Fuoss and Kraus's equilibrium constants are on a somewhat conventional scale, to which we have adhered: a value for the limiting conductance, Λ_1°, of simple ions in standard conditions, benzene at 25°, is adopted, and therefrom values are derived for other conditions by means of Walden's rule. It is assumed that the mean mobility of triple ions, and therefore their limiting conductance, Λ_3°, is one-third of that of simple ions.

The equilibrium constants K_2 and K_3 having been determined, the electrostatic theory developed by Bjerrum and by Fuoss and Kraus permits calculation, not only of the maximum separation, q_2 and q_3, of counter-ions, but also the nominal minimum, or most stable, separation, a_2 and a_3, of their charge centres in an ion-pair and in a triple ion, respectively. For the pair, the equations,[6] between which b_2 must be eliminated, to give q_2 and a_2 are:

$$q_2 = e^2/2D\boldsymbol{k}T \qquad a_2b_2 = 2q_2 \qquad 32\pi\boldsymbol{N}q_2^3K_2Q(b_2) = 10^3$$

$$[Q(b_2) = \int_0^{b_2} x^4e^{-x}dx \text{ is tabulated}]$$

For the triple ion, b_3 and r_3 must be eliminated between the equations,

$$q_3 = a_3r_3 \qquad a_3b_3 = 2q_3 \qquad 2\pi\boldsymbol{N}a_3^3K_3I(b_3) = 10^3 \qquad b_3(1 + 2r_3) = 2r_3(1 + r_3)^2$$

with the aid of tables for

$$I(b_3) = \int_1^{r_3} dx \int_{-1}^{+1} dy \left[x^2 \exp\left\{\frac{b_3}{x(x+1)}\right\} \exp\left\{\frac{b_3}{(x+1)} \cdot \left(1 - \frac{x+1}{\sqrt{(x^2+2xy+1)}}\right)\right\}\right]$$

in order to obtain q_3 and a_3.

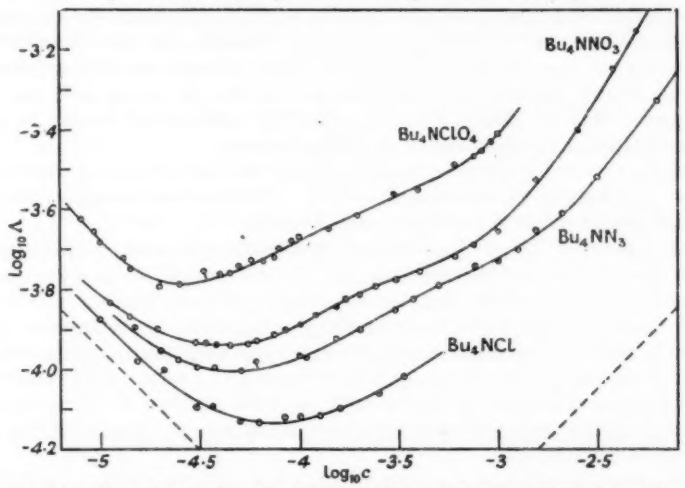
[5] Robinson and Stokes, "Electrolyte Solutions," Butterworths, London, 1955, p. 390.
[6] Harned and Owen, "Electrolytic Solutions," Reinhold Publ. Corp., New York, 1950, pp. 42—47.

(4) *Conductances of Single Tetra*-n-*butylammonium Salts.*—We have measured the conductances, in benzene at 30°, of tetra-*n*-butylammonium chloride, azide, nitrate, and perchlorate. The perchlorate has been measured before,[7] but at 25°, these measurements, according to our estimate of the solubility of the salt, having been carried into considerably supersaturated solutions, a condition which we avoided, fearing the danger of crystallisation, which can be practically invisible.

The general form of our results for the four single salts is shown in Fig. 1, as a plot of $\log_{10} \Lambda$ *versus* $\log_{10} c$. The broken line on the left has the Ostwald-law slope $-\frac{1}{2}$, which should apply when simple ions are the only carriers of the current, whilst the broken line on the right shows the slope $+\frac{1}{2}$, which should obtain if triple ions alone carried the current, provided, in either case, that nearly the whole of the salt consists of ion-pairs.

The minima all occur within the concentration range 10^{-5}—10^{-4}M: at these minima, simple and triple ions each carry one-half of the current. The magnitude of the

FIG. 1. *Plot of log* Λ versus log *c for single salts; and theoretical slopes for simple and triple ions singly in equilibrium with ion-pairs constituting almost the whole of the salt.*



(In order to reduce the number of points, only those of Series A, Table 6, are shown.)

conductances in this region shows that almost the whole of the salts consists of ion-pairs: a fraction of the order of a few millionths at most exists as simple ions, and a similarly small fraction as triple ions. As the concentration rises towards 10^{-3}M and beyond, the pairs begin to associate to give quadrupoles. As it continues to rise towards 10^{-2}M, charged higher aggregates appear in sufficient amount to render them important carriers of the current.

Some of these conclusions can be made quantitative on the basis of the electrostatic theory outlined. When we replot the conductance curves in the form $\Lambda\sqrt{c}$ *versus* c, we obtain good straight lines to about $c = 10^{-3.5}$M. Two such lines for single salts appear in each of Figs. 2 and 3. From the intercepts A and slopes B of the lines, we can compute $\Lambda_{min.}$ and $c_{min.}$, the latter more accurately than it could be read from the curves of Fig. 1. Using Fuoss and Kraus's standard and procedure, we take as the limiting equivalent conductances in benzene at 30°, $\Lambda_1^\circ = 107$, and $\Lambda_3^\circ = 35{\cdot}6$ ohm^{-1} cm.^{2} mole^{-1}. Hence we can compute the ion-pair and triple-ion dissociation constants, K_2 and K_3, and then the maximum and minimum counter-ion distances, q_2 and a_2 for the pairs, and q_3 and a_3 for the triple ions. All these values are in Table 1.

[7] Luder, Kraus, Kraus, and Fuoss, *J. Amer. Chem. Soc.*, 1936, **58**, 255.

TABLE 1. *Electrolytic constants of single tetra-n-butylammonium salts in benzene at* 30°.

	Chloride	Azide	Nitrate	Perchlorate
10^7A (A in ohm^{-1} cm.^{2} mole$^{-0\cdot5}$ l.$^{-0\cdot5}$)	3·4	3·8	3·7	5·0
10^3B (B in ohm^{-1} cm.^{2} mole$^{-1\cdot5}$ l.$^{0\cdot5}$)	4·2	7·0	9·3	15·5
$10^5\Lambda_{min.}$ (Λ in ohm^{-1} cm.^{2} mole^{-1})	7·55	10·3	11·7	17·6
$10^3c_{min.}$ (mole l.$^{-1}$)	8·1	5·4	4·0	3·2
$10^{12}K_2$ (mole l.$^{-1}$)	10·1	12·5	11·95	21·85
10^5K_3 (mole l.$^{-1}$)	2·70	1·80	1·33	1·08
q_2 (Å)	122	122	122	122
a_2 (Å)	5·8	5·8	5·8	5·8
q_3 (Å)	39	39	39	39
a_3 (Å)	8·9	8·5	8·3	8·1

It is to be observed that the power of a salt to give simple ions increases with its K_2, but that its power to give triple ions increases with decreasing K_3. Thus for the formation of simple ions, the salts become stronger in the order $Cl^- < N_3^- \sim NO_3^- < ClO_4^-$, and, for the formation of triple ions, they stand in the nearly similar order $Cl^- < N_3^- < NO_3^- < ClO_4^-$.

By the method of calculation used, q_2 is in principle the same for all uni-univalent salts; but the same is not true for a_2, q_3, and a_3. However, for the four salts treated, a_2 and q_3 come out constant to the accuracy with which they are quoted, whilst a_3 varies a little, and, as regards the two salts with isotropic anions, not in the direction one might naïvely expect. Without doubt, this is because the electrostatic theory is not a very good approximation at the short end of the distance range.

It is instructive to calculate the actual fractions of the salts, which are present as simple ions, and as triple ions, at various concentrations. This has been done, and the results are included with similar values for mixed salts in Table 3.

(5) *Conductances of Mixed Tetra-n-butylammonium Salts.*—In preparation for our mechanistic problem, we had to have some idea of the extent to which an ion-pair form of one salt could provide a stable seat for the simple anion of another, thereby possibly removing a chemically active species, or creating a chemically important new species, the unsymmetrical triple anion, whose properties could probably not be interpolated between those of the symmetrical triple anions given by the separate salts. This required a study of the conductances of mixed salts, and a solution of the problem of extracting from such results the dissociation constants of unsymmetrical triple ions. Studies of this kind seem not to have been made before.

We have set up the problem in a form, which is not only the simplest possible, but also probably the most accurate for the purpose in view, by measuring the conductances of binary mixtures, which are equimolar, and remain so with changing total salt concentration. We shall set down the method of deriving the new equilibrium constants from conductance data for this especially simple case.

The following eight equilibria require to be considered :

$$M^+X^- \rightleftharpoons M^+ + X^- \qquad K_{2x} = [M^+][X^-]/[M^+X^-]$$

$$M^+Y^- \rightleftharpoons M^+ + Y^- \qquad K_{2y} = [M^+][Y^-]/[M^+Y^-]$$

$$M^+X^- + M^+ \rightleftharpoons M^+X^-M^+ \qquad K_{3x} = [M^+X^-][M^+]/[M^+X^-M^+]$$

$$M^+X^- + X^- \rightleftharpoons X^-M^+X^- \qquad = [M^+X^-][X^-]/[X^-M^+X^-]$$

$$M^+Y^- + M^+ \rightleftharpoons M^+Y^-M^+ \qquad K_{3y} = [M^+Y^-][M^+]/[M^+Y^-M^+]$$

$$M^+Y^- + Y^- \rightleftharpoons Y^-M^+Y^- \qquad = [M^+Y^-][Y^-]/[Y^-M^+Y^-]$$

$$M^+X^- + Y^- \rightleftharpoons X^-M^+Y^- \qquad K_{3xy} = [M^+X^-][Y^-]/[X^-M^+Y^-]$$

$$M^+Y^- + X^- \rightleftharpoons X^-M^+Y^- \qquad K_{3yx} = [M^+Y^-][X^-]/[X^-M^+Y^-]$$

There is one relation between the six equilibrium constants thus defined, *viz.* :

$$K_{3yx}/K_{2x} = K_{3xy}/K_{2y}$$

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We have therefore five independent equilibrium constants, of which four can be evaluated from the conductances of the pure salt, leaving the fifth to be derived from the conductance of the mixture. The above relation also means that we have set down so far, not eight, but seven independent relations between the concentrations of the chemical species. However, charge balance provides the additional relation,

$$[M^+] + [M^+X^-M^+] + [M^+Y^-M^+] = [X^-] + [Y^-] + [X^-M^+X^-] + [Y^-M^+Y^-] + [X^-M^+Y^-]$$

and material balance two further relations, which can be simplified to

$$[M^+X^-] = [M^+Y^-] = c/2$$

because the fractional extent to which current-carrying ions are present is very small. Thus we have $8 - 1 + 1 + 2 = 10$ independent relations, of which 2 directly express the ion-pair concentrations, whilst the other 8 permit us to calculate the concentrations of the three simple ions and five triple ions.

The result of this calculation can be the more conveniently expressed if we first introduce some auxillary quantities. First, we define certain combinations of the equilibrium constants, *viz.*, the arithmetic K_2 mean, a harmonic K_3 mean, and three K_2/K_3 ratios, and their sum :

$$K_{2m} = \tfrac{1}{2}(K_{2x} + K_{2y}) \qquad K_{3M}^{-1} = \tfrac{1}{2}(K_{3x}^{-1} + K_{3y}^{-1})$$

$$\rho_x = K_{2x}/K_{3x} \qquad \rho_y = K_{2y}/K_{3y} \qquad \rho_{xy} = K_{2x}/K_{2yx} = K_{2y}/K_{3xy}$$

$$S = \rho_x + \rho_y + \rho_{xy}$$

All K's have the dimensions of concentration. We now define a pure number F in terms of the above K combinations, and of the concentration c :

$$F = \left\{1 + \frac{cS}{4K_{2m}}\right\}^{\frac{1}{2}} \cdot \left\{1 + \frac{c}{K_{3M}}\right\}^{-\frac{1}{2}}$$

Finally, we define a concentration R in terms of F :

$$R = (cK_{2m})^{\frac{1}{2}} \, . \, F$$

The concentrations of the simple and triple ions can now be expressed as follows :

$$[M^+] = R$$

$$[X^-] = cK_{2x}/2R$$

$$[Y^-] = cK_{2y}/2R$$

$$[M^+X^-M^+] = cR/2K_{3x}$$

$$[M^+Y^-M^+] = cR/2K_{3y}$$

$$[X^-M^+X^-] = c^2K_{2x}/4RK_{3x}$$

$$[Y^-M^+Y^-] = c^2K_{2y}/4RK_{3y}$$

$$[X^-M^+Y^-] = c^2K_{2x}/4RK_{3yx} = c^2K_{2y}/4RK_{3xy}$$

This allows us to derive the equation for the curve of the equivalent conductance of the mixed salts, taking into account all species up to triple ions. Basically the equation is :

$$\overline{\Lambda} = \Lambda_1^\circ\phi_1 + \tfrac{1}{3}\Lambda_3^\circ\phi_3$$

when ϕ_1 is the fraction of total salt present as simple ions, and ϕ_3 is the fraction present as triple ions. (The coefficient $\frac{1}{3}$ arises because complete conversion of the pairs could make only $\frac{1}{3}$ as many triple ions as it could make of simple ions, whereas the limiting conductances Λ_1° and Λ_3° are each reckoned for 1 mole of cation and 1 mole of anion.)

We have above the concentrations required for computing ϕ_1 and ϕ_3. The result of this calculation is again most simply expressed with the help of the function F:

$$\phi_1 = \left(\frac{K_{2m}}{c}\right)^{\frac{1}{2}} \cdot \frac{F^2+1}{2F}$$

$$\tfrac{1}{3}\phi_3 = \left(\frac{cK_{2m}}{K_3}\right)^{\frac{1}{2}} \cdot F + \left(\frac{K_{2m}}{c}\right)^{\frac{1}{2}} \cdot \frac{F^2-1}{2F}$$

In order to isolate, from the above equation for $\overline{\Lambda}$, the relatively simple part of it which is practically useful, we first expand the three involved F-factors in ascending powers of c. We then find that:

$$(F^2+1)/2F \text{ gives terms in } c^0, -, c^2, c^3, \ldots\ldots$$
$$F \quad ,, \quad ,, \quad ,, \; c^0, c^1, c^2, c^3, \ldots\ldots$$
$$(F^2-1)/2F \quad ,, \quad ,, \quad ,, \; -, c^1, c^2, c^3, \ldots\ldots$$

and therefore that

$$\Lambda_1{}^\circ\phi_1 \text{ contains terms in } c^{-\frac{1}{2}}, -, c^{\frac{1}{2}}, c^{\frac{3}{2}}, \ldots$$
$$\tfrac{1}{3}\Lambda_3{}^\circ\phi_3 \quad ,, \quad ,, \quad ,, \; -, c^{\frac{1}{2}}, c^{\frac{3}{2}}, c^{\frac{5}{2}}, \ldots$$

Since the equation for $\overline{\Lambda}$ contains a negative power, as well as positive powers, of c, the $\overline{\Lambda}$–c curves for mixtures will, like the Λ–c curves for pure salts, pass through a minimum. Furthermore, with mixtures, as with pure salts, the term in $c^{-\frac{1}{2}}$ is controlled exclusively by the simple ions, and that in $c^{\frac{1}{2}}$ exclusively by the triple ions. The new feature of the conductance equation of mixed salts is that the interplay of simple with triple ions now produces terms in $c^{\frac{3}{2}}$ and higher powers, which do not come into the equation for pure salts, until we take account of complexes higher than quadrupoles.

Clearly then, the practically useful equation for $\overline{\Lambda}$ is

$$\overline{\Lambda} = \overline{A}c^{-\frac{1}{2}} + \overline{B}c^{\frac{1}{2}} + \ldots$$

where $\overline{A}$ and $\overline{B}$ are to be calculated by evaluating the necessary coefficients in the above-mentioned expansions. The results of this calculation are

$$\overline{A} = \Lambda_1{}^\circ\sqrt{K_{2m}}$$

$$\overline{B} = \Lambda_3{}^\circ\left(\frac{\sqrt{K_{2m}}}{2K_{3M}} + \frac{S}{8\sqrt{K_{2m}}}\right)$$

When, from our observations, we plot $\Lambda\sqrt{c}$ against c we should get an initially straight line, characterised by an intercept $\overline{A}$ and a slope $\overline{B}$. The mean constants K_{2m} and K_{3M} being known from experiments with pure salts, $\overline{A}$ gives no new information, but $\overline{B}$ allows us to calculate the sum of ratios S; and since two of these ratios ρ_x and ρ_y are similarly known, we can deduce the remaining one, ρ_{xy}, and therefore the equilibrium constants, K_{3xy} and K_{3yx}, for the mixed triple anion.

For the equimolar salt-pairs which have been experimentally examined, the results are of the general form required by theory. We get linear plots of $\overline{\Lambda}\sqrt{c}$ versus c over nearly as wide a range as in the plots of $\Lambda\sqrt{c}$ against c for pure salts.

One such plot, apparently one of the commoner kind, is shown in Fig. 2. It is true of three of the four mixtures we have studied, of the chloride–nitrate, nitrate–perchlorate, and chloride–perchlorate mixtures, that the $\Lambda\sqrt{c}$ curve for the mixture lies much nearer the more steeply sloping of the curves for the pure components. This tells us qualitatively that the mixtures are making a better-than-statistical use of their additional opportunities of forming triple ions, and are therefore probably generating a more-than-statistical proportion of the mixed triple anion.

XUM

The exceptional mixture is chloride–azide, the plot for which is shown in Fig. 3. The curve for this mixture lies almost midway between the curves for the pure components. This means that total triple ions, and therefore probably mixed triple anions, are being produced only in roughly the statistical amounts, *i.e.*, that there is no large specific tendency to the formation of this particular mixed triple anion. Of course, any such specific tendency must depend in some way on a chemical difference between the constituent simple anions, since it disappears when they become identical. With respect to this form of difference, it would seem that chloride and azide are more alike, than are chloride and either of the oxy-anions, or than are the oxy-anions themselves.

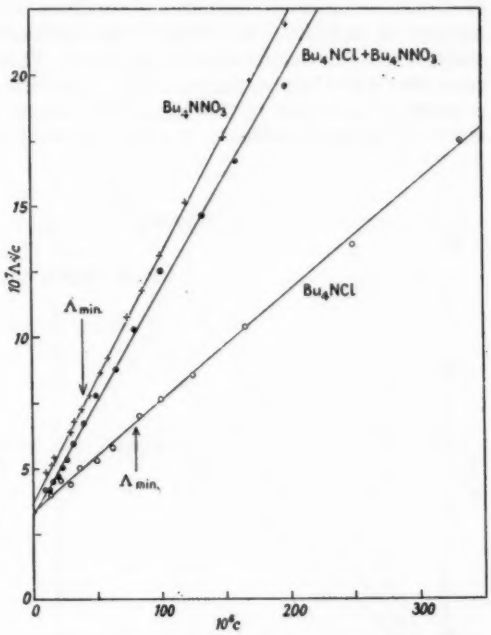

FIG. 2. *Plots of* $\Lambda\sqrt{c}$ versus c *for tetra*-n-*butylammonium chloride and nitrate and their equimolar mixture.*

(Points from Series A of Table 6.)

The values of $\overline{A}$ and $\overline{B}$ found in these experiments, and some of the intermediate figures obtained from them and from the data for pure salts, as well as the derived values of K_{3xy} and K_{3yx} (which are the objects of the exercise), are given in Table 2.

TABLE 2. *Electrolytic constants of equimolar binary mixtures of tetra*-n-*butylammonium salts in benzene at* 30°.

X^- / Y^-	Cl^- / N_3^-	Cl^- / NO_3^-	Cl^- / ClO_4^-	NO_3^- / ClO_4^-
Observational results for mixed salts:				
$10^7\overline{A}$ (ohm^{-1} cm.^{2} mole$^{-0.5}$ l.$^{0.5}$)	3·6	3·3	5·5	4·7
$10^8\overline{B}$ (ohm^{-1} cm.^{2} mole$^{-1.5}$ l.$^{0.5}$)	5·35	8·6	14·2	14·9
Calculated from data on pure salts:				
$10^{10}\ K_{2xx}$ (mole l.$^{-1}$)	11·8	11·0	16·0	16·9
$10^{-5}/K_{2M}$ (mole l.$^{-1}$)	0·463	0·561	0·648	0·839
$10^7\overline{A}$ (ohm^{-1} cm.^{2} mole$^{-0.5}$ l.$^{0.5}$)	3·6	3·5	4·3	4·4
Calculated from data on mixed salts:				
$10^{12}S$	19·6	39·4	86·1	81·1
10^5K_{3xy} (mole l.$^{-1}$)	1·405	0·447	0·349	0·421
10^5K_{3yx} (mole l.$^{-1}$)	1·135	0·378	0·161	0·230

XUM

The agreement between the found and the calculated $\overline{A}$ values is fair or good for three of the mixtures, though for one there is a marked discrepancy. However, $\overline{A}$ and A values depend on an extrapolation influenced mainly by conductance measurements at the dilute end of the concentration range, and, calculated in terms of equivalent conductance, these are the least accurate of the measurements. The slopes $\overline{B}$ and B are much more certain, and it is with these that we are now concerned.

When we compare the K_{3xy} and K_{3yz} values in Table 2 for the mixed triple anions chloride–nitrate, chloride–perchlorate, and nitrate–perchlorate, with the K_3 values for any of the four symmetrical triple anions, as given in Table 1, we see a general difference of about one order of magnitude: smallness of dissociation constant being taken as a measure of stability, these three unsymmetrical triple ions are roughly ten times more stable than the symmetrical triple ions. There are individual differences, which are consistent with the idea that an excess of stability in the mixed triple ion is connected with a stability difference in the component simple anions. The chloride–perchlorate triple anion is the most stable, then comes nitrate–perchlorate, and then the chloride–nitrate.

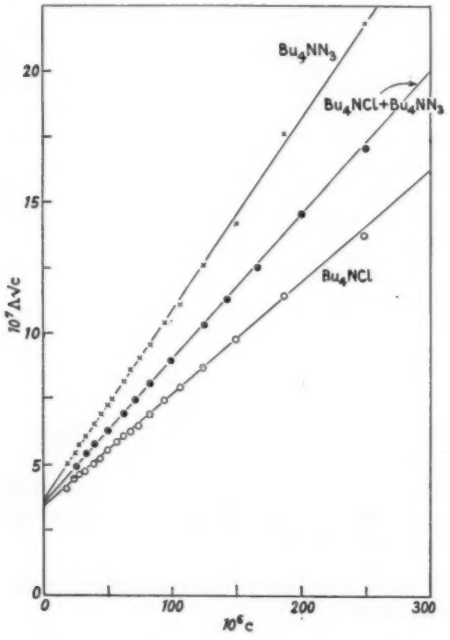

FIG. 3. *Plots of* $\Lambda\sqrt{c}$ versus c *for tetra-n-butylammonium chloride and azide and their equimolar mixture.*

(Points from Series B of Table 6.)

Last, by a long way, comes the chloride–azide anion, which is of the same order of stability as any of the four symmetrical triple ions, though it is actually somewhat more stable than either the chloride triple ion or the azide triple ion.

It is interesting to note in what directions the unsymmetrical triple ions prefer to break up. The chloride–perchlorate ion prefers to drop off a perchlorate ion, the nitrate–perchlorate a perchlorate, the chloride–nitrate a nitrate, and the chloride–azide an azide ion. Thus the competitive success in separation of simple anions from mixed triple anions stands in the order $ClO_4^- > NO_3^-, N_3^- > Cl^-$. We have seen that the ease of separation of simple anions from ion pairs has the order $ClO_4^- > NO_3^- \sim N_3^- > Cl^-$; and that their ease of splitting from symmetrical triple ions is in the order $ClO_4^- > NO_3^- > N_3^- > Cl^-$; and, finally, that if the stability of mixed triple anions depends on the difference in a

property of the component simple anions, then that property places them in the order $ClO_4^- > NO_3^- > N_3^- \sim Cl^-$.

A word should be said about the accuracy of the mixed-ion constants K_{3xy} and K_{3yx}, inasmuch as they are calculated by difference. For the three especially stable mixed anions, chloride–nitrate, chloride–perchlorate, and nitrate–perchlorate, the point scarcely arises; for ρ_{xy} is much the most important term in the sum S, and the S-term is the main term in the formula for $\overline{B}$. For the chloride–azide anion, ρ_{xy} supplies about one-half of S, and the S-term about one-half of $\overline{B}$; and so the difference character of the calculation multiplies the error by 4. On the other hand, the $\Lambda\sqrt{c}$ plots for chloride, for azide, and for the mixture were very good, and were, indeed, the best we had, and we therefore think that the constants for this particular mixed anion may be no worse than those for the others.

We have now all the equilibrium constants necessary for calculating the concentrations of any or all the ionic species present at any concentration of mixed salts below those at which quadrupoles and higher aggregates are formed in quantity. We can, of course, do the same calculation for the component pure salts, and so discover what happens to the various species when two salts are mixed. In Table 3, the results of such calculations are

TABLE 3. *Ionic fractions in millionths* ($10^6 f$) *for simple and triple ions at various stoicheiometric concentrations* (c) *of tetra*-n-*butylammonium salts*, MX, MY, *and of their equimolar mixtures*, $\frac{1}{2}$(MX + MY), *in benzene at* 30°.

	$c = 10^{-6}$M			$c = 10^{-5}$M			$c = 10^{-4}$M			$c = 10^{-3}$M		
	X	$\frac{1}{2}$(X + Y)	Y	X	$\frac{1}{2}$(X + Y)	Y	X	$\frac{1}{2}$(X + Y)	Y	X	$\frac{1}{2}$(X + Y)	Y
(1) Chloride (X), azide (Y), mixture {$\frac{1}{2}$(X + Y)}.												
M^+	3·18	3·38	3·54	1·00	1·06	0·12	0·32	0·33	0·35	0·10	0·10	0·11
X^-	3·18	1·49	—	1·00	0·48	—	0·32	0·15	—	0·10	0·05	—
Y^-	—	1·86	3·54	—	0·59	0·12	—	0·19	0·35	—	0·06	0·11
M_2X^+	0·12	0·06	—	0·37	0·19	—	1·18	0·62	—	3·72	1·90	—
M_2Y^+	—	0·09	0·20	—	0·29	0·62	—	0·92	1·97	—	2·85	6·21
MX_2^-	0·12	0·03	—	0·37	0·09	—	1·18	0·29	—	3·72	0·91	—
MY_2^-	—	0·05	0·20	—	0·16	0·62	—	0·53	1·97	—	1·68	6·21
MXY^-	—	0·07	—	—	0·22	—	—	0·69	—	—	2·17	—
(2) Chloride (X), nitrate (Y), mixture {$\frac{1}{2}$(X + Y)}.												
M^+	3·18	3·37	3·46	1·00	1·16	1·09	0·32	0·41	0·35	0·10	0·13	0·11
X^-	3·18	1·50	—	1·00	0·44	—	0·32	0·12	—	0·10	0·04	—
Y^-	—	1·77	3·46	—	0·52	1·09	—	0·15	0·35	—	0·04	0·11
M_2X^+	0·12	0·06	—	0·37	0·21	—	1·18	0·75	—	3·72	2·45	—
M_2Y^+	—	0·13	0·26	—	0·44	0·82	—	1·53	2·60	—	4·96	8·23
MX_2^-	0·12	0·03	—	0·37	0·08	—	1·18	0·23	—	3·72	0·71	—
MY_2^-	—	0·07	0·26	—	0·19	0·82	—	0·55	2·60	—	1·70	8·23
MXY^-	—	0·20	—	—	0·58	—	—	1·64	—	—	5·06	—
(3) Chloride (X), perchlorate (Y), mixture {$\frac{1}{2}$(X + Y)}.												
M^+	3·18	4·13	4·67	1·00	1·51	1·48	0·32	0·56	0·47	0·10	0·18	0·15
X^-	3·18	1·22	—	1·00	0·33	—	0·32	0·09	—	0·10	0·03	—
Y^-	—	2·65	4·67	—	0·73	1·48	—	0·19	0·47	—	0·06	0·15
M_2X^+	0·12	0·08	—	0·37	0·28	—	1·18	1·03	—	3·72	3·37	—
M_2Y^+	—	0·19	0·43	—	0·70	1·37	—	2·58	4·32	—	8·43	13·70
MX_2^-	0·12	0·02	—	0·37	0·06	—	1·18	0·17	—	3·72	0·51	—
MY_2^-	—	0·12	0·43	—	0·33	1·37	—	0·91	4·32	—	2·78	13·70
MXY^-	—	0·38	—	—	1·04	—	—	2·82	—	—	8·62	—
(4) Nitrate (X), perchlorate (Y), mixture {$\frac{1}{2}$(X + Y)}.												
M^+	3·46	4·18	4·67	1·09	1·42	1·48	0·35	0·48	0·47	0·11	0·16	0·15
X^-	3·46	1·43	—	1·09	0·42	—	0·35	0·12	—	0·11	0·04	—
Y^-	—	2·62	4·67	—	0·77	1·48	—	0·23	0·47	—	0·07	0·15
M_2X^+	0·26	0·16	—	0·82	0·53	—	2·60	1·82	—	8·23	5·84	—
M_2Y^+	—	0·19	0·43	—	0·66	1·37	—	2·24	4·32	—	7·19	13·70
MX_2^-	0·26	0·05	—	0·82	0·16	—	2·60	0·46	—	8·23	1·45	—
MY_2^-	—	0·12	0·43	—	0·36	1·37	—	1·05	4·32	—	3·26	13·70
MXY^-	—	0·31	—	—	0·91	—	—	2·69	—	—	8·37	—

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given in a form in which the concentration of each kind of ion has been divided by c, the total salt concentration, to give an " ionic fraction " f. These ionic fractions, *viz.*:

$$f = \frac{\text{Concentration of one kind of ion which may be simple or triple}}{\text{Total stoicheiometric concentration of salt or salts}}$$

are small, and are conveniently expressed in millionths.

Two conclusions may be drawn from Table 3, which are significant for our kinetic studies. The first holds in all cases: it is that when two salts are mixed the simple anion of neither is unduly consumed; *e.g.*, when one-half of a salt is replaced by one with a different anion, the original simple anion is never reduced in concentration to as little as one-quarter. The second conclusion is that, when two salts are mixed, a far from complete consumption occurs of those triple anions that are formed by the separate salts, though in this there is a notable quantitative difference between the mixtures. In the chloride–nitrate, chloride–perchlorate, and nitrate–perchlorate mixtures, some 70—85% of the symmetrical triple anions may disappear to give a greatly preponderating amount of the unsymmetrical triple anion. In the chloride–azide mixture, the total of triple ions is about the mean of those given by the chloride and azide separately, and of that total, roughly one-half consists of the two symmetrical triple anions, leaving about one-half for the mixed triple anion.

(6) *Cursory Survey of Effects of Added Molecular Substances on Salt Conductances.*— Hydrogen chloride in benzene has a conductance, but it is smaller than that of any of the tetra-*n*-butylammonium salts. However, as will be seen from Table 4, the addition of hydrogen chloride raises the conductance of tetra-*n*-butylammonium chloride strongly, and of the corresponding nitrate moderately, but of the perchlorate not at all.

TABLE 4. *Reciprocal resistance* (ohm^{-1}) *of a cell containing solutions in benzene at* 30° *of tetra*-n-*butylammonium salts* (MX) *with added hydrogen chloride.*

10^4[HCl]	10^4[MX]	10^8 ohm^{-1} HCl only	10^8 ohm^{-1} Salt only	10^8 ohm^{-1} Mixture
Tetra-n-*butylammonium chloride.*				
0·40	1·92	0·02	0·17	0·33
3·0	4·55	0·10	0·55	2·08
3·3	3·84	0·10	0·41	2·00
3·4	3·57	0·11	0·38	1·87
3·6	3·33	0·11	0·36	1·74
3·8	3·12	0·11	0·34	1·60
4·0	2·00	0·12	0·18	0·93
Tetra-n-*butylammonium nitrate.*				
—	10·0	—	2·55	2·55
0·25	9·7	0·01	2·5	2·63
0·50	9·5	6·02	2·4	2·83
Tetra-n-*butylammonium perchlorate.*				
—	10·0	—	4·5	4·5
0·60	9·4	0·02	4·2	4·1
1·00	8·8	0·03	3·7	3·8

These results may be considered in conjunction with those of a preliminary survey by Dr. S. F. Mok of the effect of tetra-*n*-butylammonium chloride on the partial vapour pressure of hydrogen chloride in benzene. She found that, in concentrations of order 10^{-3}M, a strong depression of the vapour pressure occurs when the quantity of salt becomes comparable with that of the hydrogen chloride. She also found that the catalytic effect of hydrogen chloride on the methyl-alcoholysis of triphenylmethyl chloride in benzene is largely destroyed by an equivalent of added tetra-*n*-butylammonium chloride. All these results point to the conclusion that the hydrogen-dichloride ion, $(ClHCl)^-$, is very stable in benzene, and that its quaternary ammonium salts are stronger salts than are the simple chlorides. Herbrandson, Dickerson, and Weinstein have recently isolated tetramethyl- and tetraethyl-ammonium hydrogen-dichlorides from nitrobenzene solution.[8] It appears further from the conductance results that the ion $(ClHNO_3)^-$ must be moderately stable in benzene. Finally, it can be inferred that the anion $(ClHClO_4)^-$ does not exist in benzene. And this conclusion is likewise indicated by another finding of Dr. S. F. Mok, *viz.*, that

[8] Herbrandson, Dickerson, and Weinstein, *J. Amer. Chem. Soc.*, 1954, **76**, 4046.

hydrogen chloride and tetra-*n*-butylammonium perchlorate act additively in their catalysis of the methyl-alcoholysis of triphenylmethyl chloride in benzene.

For the purposes of the associated kinetic investigation, we were concerned to determine whether the presence in benzene of hydroxylic compounds in concentrations of the order of 0·1M would make any great difference to the number of simple ions produced by the ammonium salts. We therefore measured the conductance of tetra-*n*-butylammonium chloride, and that of the corresponding perchlorate, over a range of salt concentrations, in a 0·1M-solution of methyl alcohol in benzene, and in a 0·1M-solution of phenol in benzene. From the plots of $\Lambda\sqrt{c}$ *versus* c, we obtained the intercepts A and slopes B, and thence the values of $\Lambda_{min.}$ and $c_{min.}$, given in Table 5.

TABLE 5. *Electrolytic constants of single tetra*-n-*butylammonium salts in solutions of hydroxylic compounds in benzene at* 30°. [Units: A in ohm^{-1} cm.^{2} mole$^{-0.5}$ l.$^{0.5}$; B in ohm^{-1} cm.^{2} mole$^{-1.5}$ l.$^{0.5}$; $\Lambda_{min.}$ in ohm^{-1} cm.^{2} mole^{-1}; $c_{min.}$, M.]

	Chloride			Perchlorate		
	Pure C_6H_6	0·1M-MeOH in C_6H_6	0·1M-PhOH in C_6H_6	Pure C_6H_6	0·1M-MeOH in C_6H_6	0·1M-PhOH in C_6H_6
10^7A	3·4	2·7	2·0	5·0	6·0	3·2
10^3B	4·2	4·8	10·0	15·5	20·4	25·2
$10^5\Lambda_{min.}$	7·55	7·2	8·95	17·6	22·1	18·0
$10^5c_{min.}$	8·1	5·6	2·0	3·2	2·9	1·3

There is no evidence here of any very great change in the degree of dissociation of the ion-pairs. If we consider, as an example, the effect of methyl alcohol on tetra-*n*-butylammonium chloride, remembering that K_2, the equilibrium constant for the dissociation of ion-pairs to simple ions, is proportional, among other things, to A^2, it would at first sight appear that methyl alcohol slightly reduced the proportion of simple ions. This deduction would be valid only if ionic mobilities would remain the same: it is much more likely that methyl alcohol actually increases the proportion of simple ions, but solvates them, or at least solvates the chloride ion, thus decreasing ionic mobility, possibly several-fold, and at any rate in greater proportion than that in which it increases the number of the ions. Phenol, if it similarly solvated the dissociated ions, would produce a still larger electrokinetic entity, and hence a more reduced ionic mobility; and this may be the main reason why the intercept A, for both salts, drops appreciably in the presence of phenol. What we may conclude is that the proportions of simple ions are not increased very greatly by the presence of the hydroxylic compounds, probably not by more than a factor of 5 at most.

It can similarly be deduced from the figures, that the hydroxylic compounds increase the proportions of triple ions, but again by somewhat small factors.

EXPERIMENTAL

Materials.—The salts were made as described in the following paper. The benzene was dried by boiling it for one day with, and then fractionating it from, molten potassium. We found this material to be just as good as that prepared with the aid of the more recently suggested drying agent, calcium hydride.

Solubilities.—The solubilities of tetra-*n*-butylammonium chloride and perchlorate in benzene at 30° were estimated very roughly as 0·005 and 0·0005 mole/l., respectively. Tetra-*n*-butylammonium azide and nitrate are very much more soluble. The solubilities of all the salts in benzene are much increased in the presence of 0·05 or 0·1M-methyl alcohol or -benzyl alcohol.

Apparatus.—A cell was constructed by sealing, into the bottom of a 250 ml., conical flask, a cylindrical well 8 cm. deep and 2 cm. in diameter. The electrodes were two concentric platinum cylinders within the well. Measurements could then be conducted with a sample of 12 ml., which could be successively diluted up to 250 ml. In this cell, the resistance of a 0·001M-solution of potassium chloride at 25° was 59·3 ± 0·4 ohm, from which, with the aid of Shedlovsky's data,[9] the cell constant was calculated to be 0·00872. All glass apparatus was

[9] Shedlovsky, *J. Amer. Chem. Soc.*, 1932, **54**, 1411; Shedlovsky, Brown, and McInnes, *Trans. Electrochem. Soc.*, 1934, **66**, 165.

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TABLE 6. *Equivalent conductances of single and mixed tetra-n-butylammonium salts in benzene at 30°.*

10^4c	$10^4\Lambda$	10^4c	$10^4\Lambda$	10^4c	$10^4\Lambda$	10^4c	$10^4\Lambda$
			$[Bu^n_4NCl] = c$				
			Series A				
10·0	135	37·5	82·0	83·0	76·2	166	80·0
15·0	105	50·0	74·5	100	76·5	250	87·5
21·0	101	62·0	73·5	125	76·5	330	96·5
30·0	80·0						
			Series B				
18·5	94·0	44·2	78·6	75·0	74·3	125	78·0
24·2	90·0	50·0	78·3	83·3	75·2	150	80·0
27·8	87·7	57·7	76·9	94·5	76·4	187	83·5
32·6	82·8	62·5	76·6	107	76·5	250	87·0
39·5	79·3	68·2	75·3				
			$[Bu^n_4NN_3] = c$				
			Series A				
15·0	130	60·0	106	300	142	1250	199
20·0	112	100	110	375	150	1560	225
24·0	107	120	107	500	163	2080	243
30·0	103	150	119	750	183	3130	304
37·5	103	200	126	1000	187	6250	470
50·0	100						
			Series B				
18·5	117·5	44·2	104·1	75·0	104·4	125	113·0
24·2	111·3	50·0	102·7	83·3	104·4	150	116·0
27·8	109·5	53·5	102·5	94·6	106·8	187	125·4
32·6	106·7	62·5	103·0	107	107·0	250	138·0
39·5	103·5	68·2	103·2				
			$[Bu^n_4NNO_3] = c$				
			Series A				
11·3	146	45·4	116	120	138	300	168
14·3	136	54·5	117	150	144	400	176
19·5	127	60·0	119	171	151	600	194
30·3	117	75·0	124	200	155	750	207
34·0	118	85·5	127	240	163	1000	224
39·0	116	100	131				
			$[Bu^n_4NClO_4] = c$				
			Series A				
8·0	236	20·0	161	50·0	181	100	216
9·4	220	22·8	153	53·3	187	133	227
13·3	190	25·8	159	60·0	189	150	226
10·0	209	28·6	173	75·0	191	200	244
14·3	177	32·0	168	80·0	202	300	271
16·0	171	33·3	176	91·0	203	400	282
17·8	166	42·2	177				
			Series B				
23·7	165	62·5	188	100·0	205	200·0	254
36·5	176	71·5	192	125·0	218	250·0	275
50·0	181	83·3	198	166·7	240		
			$[Bu^n_4NCl] = c/2$; $[Bu^n_4NN_3] = c/2$				
			Series B				
25·0	99·2	62·5	87·8	100·0	89·6	166·6	97·3
33·3	94·0	71·5	88·8	125·0	92·5	200·0	103·5
40·0	91·4	83·3	88·8	142·8	94·5	250·0	108·0
50·0	88·8						
			$[Bu^n_4NCl] = c/2$; $[Bu^n_4NNO_3] = c/2$				
			Series A				
8·0	139	20·0	104	40·0	105	100	125
10·0	135	22·8	106	50·0	110	133	126
13·3	114	26·6	105	66·6	107	160	132
16·0	112	32·0	105	80·0	115	200	138

TABLE 6. (*Continued.*)

10^6c	$10^6\Lambda$	10^6c	$10^6\Lambda$	10^6c	$10^6\Lambda$	10^6c	$10^6\Lambda$
$[Bu^n_4NCl] = c/2$; $[Bu^n_4NClO_4] = c/2$							
Series A							
10·7	226	40·0	173	66·6	181	115	207
20·0	186	44·4	178	80·0	188	133	213
22·8	182	50·0	175	89·0	190	160	217
26·6	186	57·2	181	100	200	200	225
32·0	185						
$[Bu^n_4NNO_3] = c/2$; $[Bu^n_4NClO_4] = c/2$							
Series A							
4·0	290	16·0	176	40·0	163	133	203
5·3	261	17·8	182	53·4	171	200	215
7·1	214	20·0	172	64·0	176	266	230
8·5	218	22·8	185	80·0	182	320	241
10·0	224	26·6	168	100	192	400	251
13·0	183	32·0	162				
$[Bu^n_4NCl] = c$; [MeOH] = 0·1M.							
Series B							
25·0	76·5	62·5	72·5	100·0	74·0	200·0	87·0
40·0	71·8	71·5	73·2	125·0	78·0	250·0	92·4
50·0	71·4	83·3	73·1	166·7	81·0		
$[Bu^n_4NCl] = c$; [PhOH] = 0·1M							
Series B							
22·0	97·0	50·0	101·0	83·3	111·8	166·7	144·0
28·6	91·4	62·5	105·8	100·0	117·5	200·0	155·0
41·6	96·3	71·5	107·0	125·0	129·0	250·0	172·2
$[Bu^n_4NClO_4] = c$; [MeOH] = 0·1M							
Series B							
23·8	219	60·0	235	100·0	265	200·0	331
36·0	216	71·5	243	125·0	282	250·0	354
48·0	229	83·3	250·5	166·7	311		
$[Bu^n_4NClO_4] = c$; [PhOH] = 0·1M							
Series B							
28·6	197·5	71·5	246	125·0	314	200·0	383
48·0	221	83·3	261	166·7	348	250·0	425
60·0	235	100·0	283				

given a prolonged baking at 150° before use with the benzene solutions. The bridge had the cell as one arm, a 4-dial box of resistance 10^4 ohms as the second, a 10^6 ohm resistance as the third, and a resistance of 10^4, 10^5, 10^6, or 10^7 ohms (usually 10^5 ohms) as the fourth. A 240-volt D.C. battery supplied the current, and the poles were reversed after each reading to minimise the polarisation. A Pye-Scalamp galvanometer was employed as the null-instrument. This arrangement gave self-consistent results, though we would make no claim as to their absolute accuracy. For all measurements in benzene solution, the temperature was 30°. Each reading was repeated three or four times, sometimes more often.

Results.—These are in Table 6, apart from those already given in Table 4. The two sets of measurements, called series *A* and *B*, were made at different times, with different materials, by different experimenters. Where there was repetition, the two series led to identical values of *A* and *B*, those already quoted, and hence to identical values of all other electrolytic constants of the substances concerned.

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236. *Mechanism of Substitution at a Saturated Carbon Atom. Part LIV.* Kinetics of Chlorine Exchange between Triphenylmethyl Chloride and Tetra-n-butylammonium Chloride in Benzene.*

By E. D. Hughes, C. K. Ingold, (Miss) S. F. Mok, S. Patai, and Y. Pocker.

The kinetics are studied of the exchange of chlorine between triphenylmethyl chloride and tetra-*n*-butylammonium radiochloride in benzene at 25—45°. In these conditions the reaction is of first order in triphenylmethyl chloride, and of zeroth order in the salt at all concentrations up to saturation.

This kinetic form and rate are practically unaffected by added tetra-*n*-butylammonium perchlorate, which undergoes no stoicheiometric reaction with triphenylmethyl chloride. But the kinetic form is changed, and the initial rate is reduced by added tetra-*n*-butylammonium azide, which concurrently produces the relatively inert substance, triphenylmethyl azide, though not rapidly enough to preclude observation of the strong initial retardation produced by the salt. This retardation is identified as the kinetic " mass-law effect " in an S_N1-type reaction, as described in 1940 for unimolecular solvolysis and for other unimolecular substitutions.

The rate of exchange is much increased by added nitromethane or nitrobenzene, without disturbance to the first-order form of the runs. The initial rate of exchange is considerably increased by added pyridine, or tri-*n*-butylamine, though now such a disturbance arises, apparently, from reversible interaction between the triphenylmethyl chloride and the amine. The initial rate of exchange is greatly increased by added methyl alcohol, benzyl alcohol, or phenol, which, as reaction continues, produce some kinetic disturbance arising from the concurrent, relatively slow, formation of an ether. All these catalytic effects, whether by non-reacting polar solutes, such as the nitro-compounds, or by reacting ones, such as the hydroxy-compounds, have the common characteristic that, notwithstanding a contrary report by Swain and Kreevoy, they display no integral kinetic order which remains uniform over a significant concentration range. The number and position of these catalyst molecules in the transition state of the rate-controlling step of the measured process are thus capable of correct description only in the statistical terms appropriate to macroscopic co-solvent effects, and there is no necessary and unique placing of a single molecule of catalyst, as is required by Swain's " push-pull " theory.

It was verified that in the presence of added methyl alcohol the zeroth order of exchange with respect to tetra-*n*-butylammonium chloride is preserved. Added tetra-*n*-butylammonium perchlorate now appears to have a mildly retarding effect on the exchange.

Some part of the significance of these results is indicated, and further comment on them is made in the comparative discussion in Part LVIII.

Our object being to discover what happens to a nucleophilic substitution with a very strong tendency to use the unimolecular mechanism, S_N1, when it is transferred to an ionophobic solvent, *i.e.*, a solvent which can barely support free ions, we should probably in any case have elected to study the kinetics of the nucleophilic substitutions of triphenylmethyl chloride in benzene. But, in fact, this choice of a system for investigation was settled for us by the circumstance that the general field was not a clear one. For eight years, publications have been appearing on this particular group of reactions, and a series of statements has been made about their kinetic orders, from which conclusions have been drawn as to their mechanism, and, by extension, as to the mechanism of nucleophilic substitutions in general. And as these more general conclusions have been held to overthrow the picture of nucleophilic substitution previously set up by two of us, we

* Part LIII, preceding paper.

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felt we ought to form an opinion as to how far the kinetic descriptions given were accurate, and to what extent they supported the body of conclusions which had been built on them.

Following our paper on the electrolytic condition of salts in benzene, we now present four papers recording severally our version of the kinetics of four nucleophilic substitutions of triphenylmethyl chloride in benzene, first, two substitutions by anionic reagents, and then, two by reagent molecules. Our exploration of the electrolytic situation assists interpretation of the kinetic evidence relating to the anion substitutions. This study in turn prepares the way for the problem of the kinetics of the molecular substitutions, our interpretation of which makes use of the preceding electrochemical plus kinetic experience. The four kinetic papers, of which this is the first, are mainly concerned with description and classification, *i.e.*, with kinetics, and only to a small extent with conclusions concerning mechanism, since some repetition is avoided by dealing, as we do, with the common features of interpretation in a separate paper (Part LVIII), where we attempt to synthesise from them a partial picture of ionic reactions in benzene.

We start here with the simplest of the nucleophilic substitutions, the " symmetrical " substitution of halogen exchange between triphenylmethyl chloride and isotopically labelled chloride ion, supplied in the form of a quaternary ammonium chloride. This reaction has been investigated previously by Swain and Kreevoy,[1] who employed as their salt dimethyldi-*n*-octadecylammonium chloride, which they were not able to get even analytically pure, and therefore, as we would think, not nearly pure enough for reliable reaction kinetics. Another obvious comment on this salt is that, having the structure of a cationic soap, its properties as an electrolyte, which they did not determine, might not be completely normal. However, with this material, the rate of halogen exchange was found to be independent of its lowest concentrations, but then at a certain point to start rising with the 3·7th power of the concentration.

Preferring to use an isotropic and smaller cation, we supplied chloride ion as tetra-*n*-butylammonium chloride, the anion of which contained ^{36}Cl, so that the reaction of exchange could be followed radiochemically.

(1) *Kinetic Form of the Exchange Reaction.*—The kinetics of the exchange in benzene were studied at 25—45°. The uptake of radioactive chlorine by the triphenylmethyl chloride was of first order in triphenylmethyl chloride, and first-order constants, $k_1 = d[R^*Cl]/[RCl]dt$, did not depend on the concentration of that substance. These first-order rates were also independent of the concentration of tetra-*n*-butylammonium chloride

TABLE 1. *Rate-constants (k_1 in sec.$^{-1}$) of exchange of chlorine between triphenylmethyl chloride* (RCl) *and tetra*-n-*butylammonium radiochloride* (M^+Cl^-) *in benzene.*

Run	[RCl]	[M^+Cl^-]	10^5k_1	Mean	Run	[RCl]	[M^+Cl^-]	10^5k_1	Mean
		At 25·0°					*At* 30°		
M 81	0·01	0·00078	0·258		P 41	0·02	0·00250	0·533	
M 84	,,	0·00114	0·350		P 10	0·05	0·00150	0·503	
M 82	,,	0·00206	0·333		P 6	,,	0·00250	0·490	
M 83	,,	0·00378	0·300		P 8	,,	,,	0·475	
M 98	,,	0·00390	0·342		P 13	,,	,,	0·500	
M 80	,,	0·00393	0·308		P 34	,,	,,	0·547	
M 72	0·05	0·00250	0·352	0·320	P 35	,,	,,	0·483	
		At 44·6°			P 5	,,	0·00500	0·500	
M 102	0·05	0·00250	1·68		P 7	,,	,,	0·495	0·503
M 103	,,	,,	1·67						
M 104	,,	,,	1·70	1·68					

over an experimental range, limited on the low side by the requirements of accuracy, and on the high side by the solubility of the salt. Thus the reaction is of zeroth order in salt. We shall attach significance in Part LVIII, not only to the form of the result, but also to the absolute values of the rates, and both are illustrated in Table 1.

[1] Swain and Kreevoy, *J. Amer. Chem. Soc.*, 1955, **77**, 1122.

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The mean rate constants fit the Arrhenius equation $k_1 = B \exp(-E/\boldsymbol{R}T)$ with $B = 1{\cdot}7 \times 10^6$ sec.$^{-1}$, and $E = 16{\cdot}0$ kcal./mole. The low B value points to a transition state with a precisely defined, and probably somewhat elaborate, geometry, which, along with the consequent constitution of E, is discussed in Part LVIII.

(2) *Kinetic Effects of Added Salts.*—We have examined the effect on exchange rate of three classes of added substances, *viz.*, salts, dipolar aprotic molecules, and hydroxylic compounds. First, as to salts, we have used two, tetra-*n*-butylammonium perchlorate, which does not engage in any stoicheiometric reaction with triphenylmethyl chloride, and tetra-*n*-butylammonium azide, which reacts to produce the relatively inert substance, triphenylmethyl azide. In our conditions, the saline perchlorate has no appreciable influence, either on the kinetic form of the exchange reaction or on its rate. On the other hand, the saline azide both reduces the exchange rate, and introduces a side-reaction. The side-reaction arises because the azide converts some of the triphenylmethyl chloride into unreactive triphenylmethyl azide, and non-radioactive chloride ion. However, the interesting point is that the *initial* rates of exchange are reduced by the added azide. The results in Table 2 will illustrate these points.

TABLE 2. *Effects of added salts* (M^+X^-) *on rate constants* (k_1^a *in sec.*$^{-1}$) *of exchange of chlorine between triphenylmethyl chloride* (RCl) *and tetra*-n-*butylammonium radiochloride* (M^+Cl^-) *in benzene at* 30°.

Run	[RCl]	[M^+Cl^-]	[M^+X^-]	$10^5k_1^a$ (obs.)	$10^5k_1^a$ (calc.)
Without added salts (steady first-order rate):					
Table 1	0·02—0·05	0·0015—0·0050	—	0·503	—
Added tetra-n-*butylammonium perchlorate (steady first-order rate):*					
P 12	0·05	0·0025	0·00020	0·495	—
Added tetra-n-*butylammonium azide (initial rates cited):*					
P 32	0·05	0·0025	0·0025	0·25	0·25
P 31	0·05	0·0025	0·0125	0·07	0·08
P 42	0·02	0·0025	0·0040	0·18	0·19
P 43	0·02	0·0040	0·0040	0·30	0·25

The result last mentioned shows that radiochloride ion and azide ion are not separately attacking triphenylmethyl chloride molecules, or anything else that is freely available at the rate at which they can attack it. Obviously, the two anions are competing for something in limited supply. This competition is of the same nature as what was called the kinetic " mass-law effect " in the unimolecular mechanism of substitution, S_N1, as described in 1940 for the solvolysis of benzhydryl (diphenylmethyl) halides in aqueous acetone,[2] and for non-solvolytic substitutions of these halides in solvent sulphur dioxide,[3] and as predicted then for substitutions of triphenylmethyl halides.[4] Swain, Scott, and Lohmann subsequently observed it in the latter field, but describe their observations as if unaware of the precedents.[5] Essentially, the effect consists in the retardation of a reaction, rate-controlled by the production of an active form, when the reagent, which, left to itself, would consume the whole of this in completing the reaction being measured, finds a competitor, added or arising, with which it must contend. The simplest way in which one could demonstrate this type of effect in a radiochemically followed chloride-ion exchange, is to add a chemically different, irreversibly acting, anion, and note whether the initial rate of exchange is affected.

There must be some ratio of the specific rates of attack of chloride ion and of azide ion on the active intermediate. An assumption that this ratio is unity gives a fair account of the rate reductions, as can be seen from the last column of Table 2, where the figures are

[2] Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 979.
[3] Bateman, Hughes, and Ingold, *J.*, 1940, 1017.
[4] *Idem, ibid.*, p. 960.
[5] Swain, Scott, and Lohmann, *J. Amer. Chem. Soc.*, 1953, **75**, 136; cf. also ref. 1.

computed on that basis. Bearing in mind the considerable experimental error in initial rates, it is suggested only that the ratio may be taken as unity to within ±20%.

The above means, for example, that if we add azide ion in quantity equivalent to the chloride ion, the rate of chloride exchange is cut by about one-half, and that if we add five times as much, it is cut to about one-sixth. It would be easy at this point to jump to the conclusion that the loss of rate is equal to the rate of the concurrent formation of triphenylmethyl azide; but that is not so. It will be shown in the next paper (Part LV, Section 1) that this azide is in fact formed much more rapidly, though its formation rate is in turn cut by an added saline chloride according to a law of just the same form. Moreover, the concurrent chloride exchange, thereby permitted, has a rate much smaller than would be equivalent to the loss in the rate of formation of triphenylmethyl azide. The meaning of these apparent paradoxes is considered in Part LVIII (Section 2).

(3) *Kinetic Effect of Added Non-hydroxylic Polar Molecules.*—As rate-influencing molecular substances of the polar but non-hydroxylic class, we investigated two nitro-compounds and two tertiary amines. Nitromethane and nitrobenzene accelerate the chlorine exchange, without disturbing the first-order form of the runs. However, no simple relation is revealed by the results in Table 3, between the rate increase and the

TABLE 3. *Effect of added polar aprotic solutes* (PA) *on rate constants* (k_1^{pa} *in sec.*$^{-1}$) *of exchange of chlorine between triphenylmethyl chloride* (RCl) *and tetra*-n-*butylammonium chloride* (M^+Cl^-) *in benzene.*

Run	Temp.	[RCl]	[M^+Cl^-]	[PA]	$10^5k_1^{pa}$
No added substances (*steady first-order rates*) :					
Table 1	25°	0·01—0·05	0·0008—0·0025	—	0·320
,,	30	0·02—0·05	0·0015—0·0050	—	0·503
Added nitromethane (*steady first-order rates*) :					
M 65	25°	0·10	0·0026	1·09	15·8
M 66	,,	,,	0·0025	2·18	64·5
M 67	,,	,,	,,	3·27	~470
P 29	30	0·05	,,	0·37	2·67
Added nitrobenzene (*steady first-order rates*) :					
M 15	25°	0·01	0·0025	0·05	0·53
M 55	,,	,,	,,	0·20	1·34
M 54	,,	,,	,,	0·39	1·67
M 52	,,	0·04	,,	0·97	2·30
M 59	,,	0·09	,,	1·95	5·67
M 60	,,	0·01	,,	3·90	35·2
M 63	,,	,,	0·0050	,,	31·7
M 61	,,	,,	,,	4·87	89
M 62	,,	0·09	,,	6·82	~520
P 30	30	0·05	0·0025	0·97	2·90
Added pyridine (*falling specific rates* : *initial value cited*) :					
M 22	25°	0·10	0·0025	0·10	0·88
Added tri-n-*butylamine* (*falling specific rates* : *initial value cited*) :					
M 38	25°	0·10	0·0025	0·10	1·36

concentration of nitro-compound producing it. For example, if we plot the logarithm of the excess rate in the presence of nitrobenzene against the logarithm of the nitrobenzene concentration, we obtain a smoothly curving plot with no suggestion of linearity at any integral gradient: the reaction has no "kinetic order" with respect to nitrobenzene. We conclude that we are dealing with a transition state, which the polar solute stabilises in a statistical way, without accepting any close or precise placing in the transition state. In other words, we are observing a macroscopic co-solvent effect by a dipolar substance on a polar reaction.

Added pyridine and tri-*n*-butylamine increase the initial rate of chlorine exchange, but cause the specific rate of the continuing reaction to fall progressively. Interesting changes

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are observed when the triphenylmethyl chloride and tertiary base are pre-mixed, before the radioactive salt is added and the measurements are commenced. In the case of pyridine, the initial rate is reduced, but the specific rate of the continuing reaction falls much less steeply. In the case of tri-*n*-butylamine, the initial rate is further increased by this procedure. There is undoubtedly a reaction, probably a reversible one, between the triphenylmethyl chloride and the tertiary amines, to give materials, presumably quaternary ammonium salts, with different potentialities from that of the original triphenylmethyl chloride, for conversion into triphenylmethyl radiochloride. The forward rates of the reactions with the amines must be comparable to the rate of chlorine exchange of triphenylmethyl chloride. If we assume that triphenylmethyl radiochloride is formed less easily from the pyridine product, but more easily from the tri-*n*-butylamine product, than from original triphenylmethyl chloride, and also that the tertiary bases exert a dipolar co-solvent catalysis, analogous to that of the above nitro-compounds, then the whole rather complicated set of results can be understood. In the reaction with pyridine, for example, the catalysis causes the reaction to start more rapidly even though some material is being concurrently side-tracked. This side-tracking produces a progressive radioactive-dilution of chloride ion, and that is why the *apparent* specific rate of the continuing reaction falls. If we pre-mix the triphenylmethyl chloride and the base, this last disturbance will already have had much of its effect before measurements are commenced. We do not describe these experiments in detail, because the reaction they are elucidating is to be the subject of a future paper. Just two runs are cited in Table 3 to show that, in spite of the side-tracking of triphenylmethyl chloride by reaction with the tertiary bases, the initial rate of chlorine exchange is increased in their presence. In these runs, opportunity for preliminary interaction was reduced to a minimum by adding the triphenylmethyl chloride last.

(4) *Kinetic Effect of Added Alcohols and Phenol.*—We have examined the kinetic effect on halogen exchange of three added hydroxy-compounds, methyl alcohol, benzyl alcohol, and phenol. All these substances react with triphenylmethyl chloride to produce, reversibly, triphenylmethyl ethers and hydrogen chloride. In their forward direction, these reactions are slower than the chlorine exchange. Thus in the presence of 0·1M-methyl alcohol, the methyl-alcoholysis (*i.e.*, ether formation) has a rate of only one-eighth of that of the chlorine exchange. Benzyl-alcoholysis and phenolysis are slower still.

TABLE 4. *Effect of added hydroxy-compounds* (R′OH) *on the initial specific rates* (k_1^{ol} *in sec.*$^{-1}$) *of exchange of chlorine between triphenylmethyl chloride* (RCl) *and tetra*-n-*butylammonium chloride* (M^+Cl^-) *in benzene.*

Run	Temp.	[RCl]	[M^+Cl^-]	[R′OH]	$10^5k_1^{ol}$	Run	Temp.	[RCl]	[M^+Cl^-]	[R′OH]	$10^5k_1^{ol}$
No added substance:						*Added benzyl alcohol:*					
Table 1	25°	0·050	0·0025	—	0·32	P 36	30°	0·050	0·0025	0·002	0·88
,,	30	,,	,,	—	0·50	P 37	,,	,,	,,	0·004	1·17
						P 38	,,	,,	,,	0·008	2·0
Added methyl alcohol:						P 39	,,	,,	,,	0·016	4·2
M 97	25°	0·100	0·0041	0·002	0·48	P 40	,,	,,	,,	0·024	8·2
M 96	,,	0·098	,,	0·005	0·55	P 14	,,	,,	,,	0·050	37
M 90	,,	0·097	0·0010	0·020	2·58						
M 89	,,	0·095	0·0024	,,	1·93	*Added phenol:*					
M 88	,,	0·096	0·0041	,,	1·97	P 26	30°	0·050	0·0025	0·001	1·2
M 91	,,	0·097	0·0082	,,	1·90	P 27	,,	,,	,,	0·002	2·55
M 94	,,	0·100	0·0022	0·040	6·8	P 28	,,	,,	,,	0·003	6·7
M 92	,,	,,	0·0043	,,	7·7	P 25	,,	,,	,,	0·005	22
M 93	,,	0·098	0·0075	,,	6·1						
M 95	,,	0·101	0·0136	,,	6·0						
M 99	,,	0·099	0·0044	0·100	44·7						

Hence the disturbance that these ether-forming reactions would progressively introduce into the kinetics of the exchange process, by their consumption of triphenylmethyl chloride, can be entirely avoided by measuring initial exchange rates. A series of initial

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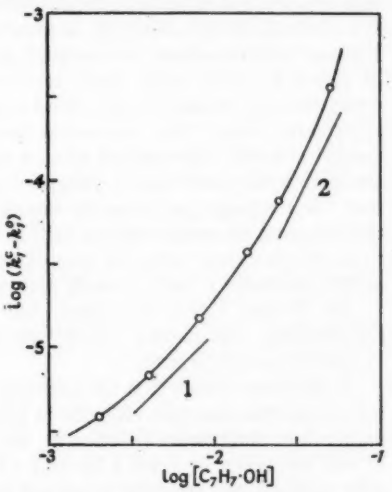
specific rates of exchange, showing the kinetic effects of the three hydroxy-compounds, are given in Table 4.

The results for the three hydroxy-compounds have the common characteristic that they indicate no particular " order " with respect to hydroxy-compound. If we plot the logarithm of the rate increase produced by added methyl alcohol, against the logarithm of the concentration of methyl alcohol, we obtain a steepening curve, with a gradient rising from zero, or a little above, to slightly more than 2, but with no visible arrest of gradient at unity, or at any other value. The rates for benzyl alcohol give a somewhat similar curve, the gradient of which rises steadily from less than 1 to more than 2, as illustrated in the Figure. The phenol curve is generally steeper, but is otherwise similar, the gradient now rising from less than 2 to about 3, without indication of an arrest.

We conclude that, like the polar aprotic solutes, these hydroxylic solutes are furnished neither in uniform small numbers, nor in precisely defined locations, to the transition



Specific rates of chlorine exchange between triphenylmethyl chloride and tetra-n-butylammonium chloride in benzene at 30° : plot of the logarithm of the rate catalysed by benzyl alcohol against the logarithm of the concentration of benzyl alcohol.

The straight lines indicate theoretical slopes for kinetic orders of 1 and 2 with respect to benzyl alcohol. Catalysis by methyl alcohol and by phenol is described similarly by smoothly bending curves.

state of the reaction stage which is rate-controlling for the measured process. The numbers and positions of these kinetically accessory molecules are in principle capable only of statistical description. The forces by which they stabilise the polar transition state must be electrostatic, and must be exerted from varying distances, as is not difficult to understand when one realises how far electrostatic forces can extend in the benzene solvent (preceding paper). This is just the type of kinetic effect which we classify as a macroscopic co-solvent effect.

The only one of these catalytic effects on which Swain and Kreevoy report is that of phenol; and their description of it differs from ours. Their claim is that the increase of rate obeys a simple second-order law,

$$\text{Rate} = k_2[\text{RCl}][\text{PhOH}]$$

said to be valid for salt up to 0·007M, and phenol up to 0·011M; *i.e.*, the order is unity in phenol. No numerical data are offered in substantiation of this statement, which our results do not support. But the equation is set down, and it is emphasised verbally that the catalysed rate is proportional to the first power of phenol concentration over a considerable range; and then these unsupported statements are used as a starting point for the development of a theory of mechanism. Anticipating some of the following papers, we may mention that this is only one of a number of allegedly simple and exact reaction-orders, which Swain has claimed to have established, and has made the foundation of his

mechanistic theories, but which are not confirmed in the present re-investigation. In one of Swain's papers it is argued,[6] that catalytic effects of hydroxy-compounds definitely cannot be co-solvent effects, " because the benzene is in more than a hundred-fold excess over the hydroxy-compound." It is added that they therefore " must be due to the termolecular mechanism " (which Swain regards as universal). This is W. Taylor's argument over again [7] (except that Taylor wanted to make the bimolecular mechanism universal). We thought that an unmistakable reply had been made to this,[8] but the general pattern of Taylor's papers is nevertheless reproduced in those of Swain.*

For the purpose of interpreting our investigations, described in accompanying papers, of the kinetics of the ether-forming reactions of triphenylmethyl chloride, we had to know whether the addition of the alcohols needed as reagents, would, or would not, seriously modify the zeroth-order character, with respect to salt, of the exchange of chlorine between triphenylmethyl chloride and an added saline chloride. Because the measured process is one of isotopic exchange, the discussion we have offered so far does not cover this point. We have, however, checked it experimentally, and two small groups of experiments, relating to kinetic order with respect to salt in the presence of methyl alcohol, are included in Table 4. They show that, for two different concentrations of methyl alcohol, the concentration of salt can be varied over a 6-fold or 8-fold range without introducing any systematic change into the initial specific rate of exchange. The reaction of triphenylmethyl chloride with methyl alcohol to give the mixed ether is considerably slower than the concurrent exchange of chlorine with an added saline chloride. Thus it would seem that the exchange preserves its kinetic form, *i.e.*, both its first order in triphenylmethyl chloride, and its zeroth order in salt, in the presence of reactive added substances, including those which greatly alter the rate of exchange, provided that the rate of reaction with the added substance is only a small, or somewhat small, fraction of the rate of exchange.

(5) *Kinetic Effect of Adding both an Alcohol and Another Salt.*—Our reason for investigating this matter will be made fully clear in Part LVIII: for the present, we explain it in outline only.

It has been shown that the exchange of chlorine between triphenylmethyl chloride and tetra-*n*-butylammonium chloride in benzene is not noticeably catalysed by tetra-*n*-butylammonium perchlorate (Section 2), but that it is catalysed by added alcohols (Section 4). It will be shown in Parts LVI and LVII that the reactions of triphenylmethyl chloride with alcohols are strongly catalysed by tetra-*n*-butylammonium perchlorate. Evidence has already been presented to show that the exchange reaction with tetra-*n*-butylammonium chloride depends on a rate-controlling step in which the saline substituting agent is not involved (Section 1). Evidence will be given, in Part LVI particularly, to the effect that the reactions with alcohols involve a rate-controlling step in which the substituting agent does not necessarily participate. Reviewing these conclusions, one naturally thinks first of the simple possibility that all the substitutions have their rates fully determined by a single common process. But, if that were so, and if that process

* A very recent case, not dealt with elsewhere in the present papers, of the tendency illustrated to assign reaction orders on totally inadequate evidence is contained in the paper by Swain, Kaiser, and Knee [9] on the nuclear alkylation of pyrrole by reaction of a triarylmethyl chloride with pyrrole in benzene. A transient colour is produced, the intensity of which was measured as a function of time and reactant concentration. The calculated curve for the rise and fall of colour fits the observational points, but in principle the calculation requires three disposable rate constants to be chosen, and in fact a fourth disposable constant, in the form of the equilibrium constant of an additional assumed equilibrium, was introduced in order to produce the fit obtained—which was then obtained despite a 4-fold discrepancy of intensity in an attempted identification of the colour source, and despite the fact that the samples of impure original chloride were coloured, with intensities up to about 70% of the maximum transient intensity measured. This unsatisfactory situation is not entirely clearly described, but is deducible from figures given.

[6] Swain, *J. Amer. Chem. Soc.*, 1948, **70**, 2989.
[7] Taylor, *J.*, 1937, 1853; 1939, 478; *J. Amer. Chem. Soc.*, 1938, **60**, 2094.
[8] Bateman, Church, and Hughes, *J.*, 1940, 913; Church and Hughes, *ibid.*, p. 920.
[9] Swain, Kaiser, and Knee, *J. Amer. Chem. Soc.*, 1955, **77**, 4681.

can be catalysed by tetra-*n*-butylammonium perchlorate, *i.e.*, by-passed by an alternative reaction-path involving the perchlorate, in the substitutions with the alcohols, then it should also be so catalysed and by-passed in the substitution with tetra-*n*-butylammonium chloride, provided that the conditions are made the same. We make the conditions the same if we study the effect of tetra-*n*-butylammonium perchlorate on the chlorine exchange reaction in the presence of, say, methyl alcohol. We have already prepared the ground for such experiments by showing (Section 4) that, in the presence of methyl alcohol, just as in its absence, the rate of chlorine exchange is independent of the concentration of tetra-*n*-butylammonium chloride. It remains, then, to determine whether this first-order reaction, when methyl alcohol is present, is catalysed by added tetra-*n*-butylammonium perchlorate. As Table 5 shows in two examples, the exchange is not catalysed by perchlorate in these conditions.

TABLE 5. *Effect of tetra*-n-*butylammonium perchlorate* ($M^+ClO_4^-$) *on the first-order rate constants* ($k_1^{p\text{-}ol}$ *in sec.*$^{-1}$) *of exchange of chlorine between triphenylmethyl chloride* (0·1M *throughout*) *and tetra*-n-*butylammonium chloride* (M^+Cl^-) *in the presence of methyl alcohol in benzene at* 25°.

Run	$[M^+Cl^-]$	[MeOH]	$[M^+ClO_4^-]$	$10^5k^{p\text{-}ol}$
M 96	0·0041	0·005	—	0·55
M 100	0·0041	,,	0·000135	∼0·53 initial, falling. 0·39 mean to 30% reaction.
M 92—M 95	0·0022—0·0136	0·040	—	6·6
M 101	0·0040	,,	0·00197	∼5·9 initial, falling. 5·0 mean to 40% reaction.

Actually, the exchange runs, in the presence of methyl alcohol and the perchlorate, start at about the rate at which they would go had the perchlorate been omitted, or perhaps somewhat more slowly, and then show a continuing retardation. Because the latter effect is superimposed on the counting fluctuations inseparable from radiochemical measurements, we cannot be quite sure that the recorded small diminution of initial rate, chiefly noticeable at the higher perchlorate concentration, is real; but it probably is, and could be understood if it were (cf. Part LVIII, Section 3). The continuing retardation is definitely real, and probably has a cause similar to that of the progressive retardation shown by the exchange reaction in the presence of pyridine (Section 3); in the present case, a concurrent methyl-alcoholysis produces chloride ion, which effects a progresive radioactive dilution of the tetra-*n*-butylammonium radiochloride, so that the rate of uptake of radioactivity by the triphenylmethyl chloride becomes diminished by a cause not taken into account in the computation of the rate constant, which accordingly falls as reaction proceeds. It is consistent that it thus falls less in the presence of more methyl alcohol, because direct measurement shows that the more methyl alcohol (above 0·002M) one adds, the less methyl-alcoholysis occurs relatively to exchange (Part LVI, Section 3), at first sight a surprising relation, which, however, can also be understood (Part LVIII, Section 3).

For the moment, the important result is that exchange is not catalysed by perchlorate, in conditions in which alcoholysis is catalysed. This shows that there is not just one rate-determining stage, which is common to both substitutions, despite the demonstrations given, and to be given, with respect to the kinetic orders of these reactions. Here we will not go beyond this negative conclusion: the positive conclusion to which the result contributes must wait until we can set other results beside it, as is done in Part LVIII.

EXPERIMENTAL

Materials.—It is convenient to describe in one place, and we choose this one, the preparation or purification of all the substances used in the work of this set of six papers, whether or not they were required for the work of the present paper.

First, as to triphenylmethyl chloride, no method of purification could be found by which

the commercial material could be used as starting point for the preparation of kinetically satisfactory samples, even though it could be very easily purified sufficiently to have the correct m. p. and give good analytical data. We therefore prepared our own triphenylmethyl chloride from methyl benzoate and phenylmagnesium bromide by way of triphenylmethanol.[10] The product was crystallised first from light petroleum–benzene containing acetyl chloride, and then repeatedly from light petroleum–benzene. The crystals were dried at 60° over phosphoric oxide in an oil-pump vacuum.

Benzene of " AnalaR " quality was refluxed for 12 hr. with, and distilled fractionally from, molten potassium. Calcium hydride was tried as a drying agent: [11] the product was as good, but not better. The main impurity in a solution of triphenylmethyl chloride, say, 0·05 or 0·1M, in benzene, as prepared for kinetics, was acid, presumably hydrogen chloride arising from adventitious moisture. With the arrangements at our disposal, we could reduce this unwanted acid to 10^{-5}M, but not lower; and some experiments were done with solutions in which it had reached higher values, 10^{-4}M or more. We therefore treated it as part of the routine in these kinetic studies to examine the effect of deliberately added hydrogen chloride on the reactions being examined, in order to assess their sensitiveness to any disturbance which might be caused by adventitious hydrogen chloride. In the experiments described in this paper, hydrogen chloride in traces is not a dangerous impurity, because it is largely inactivated as a catalyst by tetra-*n*-butylammonium chloride, which was present in all the experiments. (This effect is due to the formation of the hydrogen dichloride ion.)

The tetra-*n*-butylammonium salts were prepared from tri-*n*-butylamine (freed by the Hinsberg procedure from primary and secondary amines) and *n*-butyl iodide, both carefully fractionated before use. The quaternary iodide, crystallised from ethyl acetate–light petroleum, had m. p. 145° (Found: I, 34·35. Calc. for $C_{16}H_{36}NI$: I, 34·4%). It was converted into the nitrate with the aid of silver nitrate [12] (Found: C, 63·9; H, 12·0. Calc. for $C_{16}H_{36}O_3N_2$: C, 63·1; H, 11·8%), and into the perchlorate with silver perchlorate [13] (Found: C, 56·2; H, 10·9; N, 4·0; Cl, 10·0. Calc. for $C_{16}H_{36}O_4NCl$: C, 56·2; H, 10·6; N, 4·1; Cl, 10·4%). The last salt was another material which we found easy so to purify that it gave good analytical figures, and an m. p. close to its maximum, but difficult so to purify that it gave an unalterable minimum rate to reactions highly sensitive to catalysis. The material we found acceptable by this criterion had the characteristic that, after repeated crystallisation from ethyl acetate–light petroleum and drying for some days in an oil-pump vacuum over phosphoric oxide, the m. p. was about 199°; but that after some weeks of further drying, the m. p. rose to, and remained steady at, 203—204°. *Tetra*-n-*butylammonium azide* was made by basifying the iodide with a suspension of silver oxide in ethyl alcohol, and neutralising the solution with ethereal hydrazoic acid: after removal of the solvent under reduced pressure, the salt was obtained as a hygroscopic solid, which was precipitated repeatedly from benzene solution with light petroleum, crystallised from benzene, and given a period of prolonged drying in an oil-pump vacuum over phosphoric oxide (Found: C, 68·0; H, 13·1. $C_{16}H_{36}N_4$ requires C, 67·7; H, 12·7%). The *chloride* was similarly produced, except that the neutralisation was with aqueous hydrochloric acid, and, in so far as the radioactive chloride was required, with hydrochloric acid containing ^{36}Cl. The salt was repeatedly crystallised from light petroleum–benzene, and then was melted and kept at 100° with continued pumping in order to remove solvent of crystallisation (Found: C, 69·4; H, 13·1; Cl, 12·7. $C_{16}H_{36}NCl$ requires C, 69·2; H, 13·0; Cl, 12·8%). All these tetra-*n*-butylammonium salts crystallise from benzene in a very voluminous form containing benzene of crystallisation, which can be removed by pumping. A few experiments were made with tetraethylammonium chloride, which was crystallised from ethyl alcohol containing ether (Found: Cl, 21·4. Calc. for $C_8H_{20}NCl$: Cl, 21·4%).

Purchased nitromethane was refluxed under nitrogen with activated charcoal, and was dried, first with calcium chloride, and then with phosphoric oxide, with filtration after each stage. It was then distilled (b. p. 100·5—101·0°), passed through a column of freshly dried chromatographic alumina, then again distilled and passed through alumina. Methyl alcohol was dried in the magnesium–iodine reaction. Nitrobenzene, benzyl alcohol, and phenol, were purified conventionally. Benzyl triphenylmethyl ether, prepared from triphenylmethyl

[10] *Org. Synth.*, 1943, **23**, 98, 100.
[11] Brown, Levin, and Abrahamson, *J. Chem. Phys.*, 1951, **19**, 1226.
[12] Cox, Kraus, and Fuoss, *Trans. Faraday Soc.*, 1935, **31**, 751.
[13] Luder, Kraus, Kraus, and Fuoss, *J. Amer. Chem. Soc.*, 1936, **58**, 255.

chloride, benzyl alcohol, and triethylamine,[14] and crystallised from ethyl ether–light petroleum, had m. p. 101—102°.

Kinetic Methods.—All glass apparatus was given a prolonged baking at 150° before work with benzene solutions. The tetra-*n*-butylammonium radiochloride was weighed directly into a graduated flask, most of the benzene to be used was added, and the salt was dissolved, its dissolution being hastened by warming if necessary. Any further materials, other than triphenylmethyl chloride, to be included in the run were then added, and the solution was brought to the experimental temperature. Finally, the triphenylmethyl chloride was introduced in previously prepared benzene solution. Samples of 5 ml. were withdrawn, then and subsequently, and were run into 10 ml. of ligroin (b. p. 100—120°), which precipitated the salt completely; and after 1 min. or longer the solution was filtered through a No. 4 sintered-glass Pyrex filter. Runs in the presence of hydroxy-compounds, *e.g.*, methyl alcohol, produce some hydrogen chloride, but this is probably held back with the salt as tetra-*n*-butylammonium hydrogen-dichloride, leaving triphenylmethyl chloride as the only radioactive compound in the filtrate. The radioactivity of the filtrate was measured in a liquid-counting tube of conventional type, and then the triphenylmethyl chloride in the filtrate was determined; for some is adsorbed on the precipitated salt, and, in some experiments, a part is destroyed by a side-reaction. This measurement was made either by electrometric titration with silver nitrate after dilution with moist acetone, or by acidimetric titration with sodium hydroxide or tri-*n*-butylamine after complete hydrolysis with moist acetone, these methods giving identical results. The total radioactivity of the reaction mixture was determined by running one sample into 10 ml. of benzene, instead of ligroin, and going through the same analytical routine (except for the now unnecessary filtration).

Small modifications of this general procedure had to be introduced in certain cases. In fast runs, the ligroin was pre-cooled, in order to minimise radioactive exchange with the precipitated salt during filtration. In some runs involving nitrobenzene, more than 10 ml. of ligroin had to be used to render the precipitation of salt complete. In runs involving tri-*n*-butylamine, the triphenylmethyl chloride could be estimated by silver titration only after acidification with perchloric acid.

Rate constants, whether for a complete run or in the measurement of initial rates, were deduced from the formula:

$$k_1 = \frac{2{\cdot}303b}{(a+b)t} \log\left\{1 - \frac{x_0}{C}\left(1+\frac{b}{a}\right)\right\} \Big/ \left\{1 - \frac{x}{C}\left(1+\frac{b}{a}\right)\right\}$$

where t is the time, a and b are the concentrations of triphenylmethyl chloride and tetra-*n*-butylammonium radiochloride, respectively, x_0 and x are the counting rates, corrected for background, at the kinetic time-zero and at time t, respectively, and C is the total counting rate of the reaction mixture, corrected for background and then further corrected for the loss of triphenylmethyl chloride in the filtered samples. A convenient way to use this formula is to plot $\log\{1 - (a+b)x/aC\}$ against t, and multiply the slope of the line by $-2{\cdot}303b/(a+b)$.

TABLE 5. *Examples of chlorine-exchange runs.*

Run P 7		Run M 55		Run M 38		Run M 95	
[RCl] = 0·05M		[RCl] = 0·10M		[RCl] = 0·10M		[RCl] = 0·10M	
[Bu^n_4NCl] = 0·0050M		[Bu^n_4NCl] = 0·0025M		[Bu^n_4NCl] = 0·0025M		[Bu^n_4NCl] = 0·0136M	
In benzene at 30°		[$Ph{\cdot}NO_2$] = 0·20M		[Bu^n_3N] = 0·10M		[MeOH] = 0·040M	
C = 1760 min.$^{-1}$		In benzene at 25°		In benzene at 25°		In benzene at 25°	
		C = 80·1 min.$^{-1}$		C = 73·4 min.$^{-1}$		C = 362·0 min.$^{-1}$	
t (min.)	x (min.$^{-1}$)	t (min.)	x (min.$^{-1}$)	t (min.)	x (min.$^{-1}$)	t (min.)	x (min.$^{-1}$)
1	20	0	5·1	0	16·0	0	10·5
23	131	5	11·0	2	19·8	1	19·0
65	308	10	28·2	5	24·2	2	24·8
89	420	20	34·3	10	29·5	5	59·2
120	521	40	56·9	20	38·1	10	83·8
185	768			30	45·6	15	123·7
252	989			60	59·2	20	150·0
390	1278						

Results.—A representative selection of rate-constants is given in Tables 1—4. The type of experimental basis on which these figures rest is illustrated in Table 5. In runs M 38 and

[14] Norris and Young, *J. Amer. Chem. Soc.*, 1930, **52**, 753.

M 95, the first three points essentially determine an initial rate, since the reaction-order does not remain first throughout, owing to the progressive removal of triphenylmethyl chloride, and the progressive radioactive dilution of chloride ion, by the side-reaction involving the added substance.

Grateful acknowledgment is made to the British Council for a Travelling Fellowship granted to one of us (S. F. M.), and to the Friends of the Hebrew University and the Humanitarian Trust for a Fellowship granted to another (S. P.). We thank Mr. T. J. Collins, who greatly helped with the preparation of materials for the work described in this group of papers.

William Ramsay and Ralph Forster Laboratories,
University College, Gower St., London, W.C.1. [*Received, October 5th*, 1956.]

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237. *Mechanism of Substitution at a Saturated Carbon Atom. Part LV.* Kinetics of the Reaction of Triphenylmethyl Chloride with Tetra*-n-*butylammonium Azide in Benzene.*

By E. D. Hughes, C. K. Ingold, S. Patai, and Y. Pocker.

Contrary to Swain and Kreevoy, the reaction between triphenylmethyl chloride and a quaternary ammonium azide in benzene is not a simple second-order process, that is, one of first order in each reagent. It is approximately of first order in triphenylmethyl chloride; but, at concentrations of tetra-*n*-butylammonium azide sufficiently low to avoid a large formation of multipolar ions, the reaction is approximately of zeroth order in the salt. It is true that the first-order rate constant with respect to triphenylmethyl chloride falls as reaction continues; but that is not due to the progressive disappearance of azide ion, implying a non-zero order in azide, but to the progressive appearance of chloride ion, which exerts the mass-law retarding effect so characteristic of the S_N1 mechanism. Indeed, the reaction follows the general kinetic equation of this mechanism. Consistently, initially added tetra-*n*-butylammonium chloride reduces the initial rate, at concentrations at which added tetra-*n*-butylammonium perchlorate has no effect, and added extra tetra-*n*-butylammonium azide has scarcely any effect on the rate. The initial rate reductions are in approximately quantitative accord with the kinetic form of the continuing reaction.

Swain and Kreevoy claim that the reaction between triphenylmethyl chloride and a quaternary ammonium azide, when catalysed by phenol in benzene, is a third-order process, an example of Swain's "push-pull" mechanism, though it is stipulated that, in computing the kinetics, allowance must be made for an assumed complex between the azide and the phenol, a complex which puts the azide out of action but not the phenol. Our results reveal no definite kinetic order with respect to phenol, and no indication of the supposed complex. We conclude that there is no unique placing of just one phenol molecule in the transition state of the phenol-catalysed substitution.

These kinetic findings are discussed further in Part LVIII.

Having examined the symmetrically reversible substitution of triphenylmethyl chloride by chloride ion in benzene, we thought that the next simplest case to take up would be that of a practically irreversible substitution by some anion such as azide ion. Supplied as a quaternary ammonium azide, this anion reacts quantitatively with triphenylmethyl chloride in benzene, to produce triphenylmethyl azide, which suffers no further change in any of the conditions used in the present experiments.

* Part LIV, preceding paper.

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A kinetic description of this substitution has previously been given by Swain and Kreevoy,[1] who supplied azide ion in a sample of dimethyldi-*n*-octadecylammonium azide which was not analytically pure,* low as that standard of purity might be regarded in its application to a material intended for kinetics. Even had the salt been pure, its constitution, as a cationic soap, might have introduced uncontrolled electrolytic abnormalities. The authors describe the reaction as one of second order, *i.e.*, first order in triphenylmethyl chloride, and first order in the saline azide. They conclude that the substitution is of bimolecular type, and that a two-step mechanism, based on prior ionisation, with azide intervention in the second step, is excluded.

We supplied azide ions as tetra-*n*-butylammonium azide. We know that the electrolytic properties of this salt, in benzene at 30°, like those of the corresponding chloride, as well as those of mixtures of the two, are normal (Part LIII). This is important, because such mixtures must arise in the reaction we are to consider, *viz.*, the reaction between triphenylmethyl chloride and tetra-*n*-butylammonium azide in benzene at 30°.

Our main difficulty has been to find the region of concentration clear of those theoretical and practical obstacles that guard it like Scylla and Charybdis. For purposes of theoretical interpretation, we want a maximum of electrolytic simplicity: we would like our tetra-*n*-butylammonium azide to exist nearly wholly as one species, the ion pair, though a small proportion of quadrupoles would not matter, nor, probably, would simple and triple ions, which, although they will certainly be more chemically active than any neutral species, will be present in the extremely minute proportions illustrated in Part LIII. All this means working at considerable dilutions: it is clear, indeed, that we ought not to go up to salt concentrations much higher than 10^{-3}M. For, as Fuoss and Kraus [2] showed, the conductances of sufficiently soluble quaternary ammonium salts in benzene, a class of salt to which our azide belongs, rise sharply from 10^{-2}M to 10^{-1}M-salt, owing to the formation, in this concentration region, of charged aggregates higher than quadrupoles. At 10^{-1}M-concentration and beyond, these charged aggregates arise in considerable proportion, and, as they are very likely to be more chemically active than uncharged ion pairs, their relatively abundant formation may well lead to anomalous reaction kinetics.

That is one limitation. The counter-obstacle is that, for the purpose of getting good rate figures, *i.e.*, figures which are experimentally precise, independently of whether or not they can be interpreted, we would have liked to use these higher concentrations. Our analytical method can be made to work fairly well at salt concentrations in the neighbourhood 10^{-1}M or 10^{-2}M, but it loses accuracy at 10^{-3}M and below. Our "middle-course" has therefore been to conduct the critical kinetic experiments at azide concentrations from one to several units times 10^{-3}M. It is true that we have followed some of the kinetic phenomena into higher salt concentrations, but that was rather to see what happens when we disregard theoretically prescribed restrictions, than to obtain data for the purpose of deriving definite mechanistic conclusions. In this last matter, one is saved as usual by the circumstance that the more interesting mechanistic conclusions normally arise from the grosser kinetic phenomena, to demonstrate which high precision is not essential. The reasons why we had no need to raise these important questions of principle in the preceding paper are that the solubility of the saline reagent with which that paper deals, tetra-*n*-butylammonium chloride, is low enough to be itself a safe-guard, and that the employed radiochemical method of analysis is well suited to work at low concentrations.

(1) *Kinetic Form of the Reaction and the Effects of Added Salts.*—Unlike the reaction of

* It is recorded that one sample of the azide contained 18% of something which would not react with triphenylmethyl chloride.

[1] Swain and Kreevoy, *J. Amer. Chem. Soc.*, 1955, **77**, 1122.

[2] Fuoss and Kraus, *J. Amer. Chem. Soc.*, 1933, **55**, 3614; Luder, Kraus, Kraus, and Fuoss, *ibid.*, 1936, **38**, 255; Strong and Kraus, *ibid.*, 1950, **72**, 166.

triphenylmethyl chloride with tetra-*n*-butylammonium radiochloride, that with tetra-*n*-butylammonium azide, even at low concentrations, does not follow the simple first-order rate law. First-order constants, k_1, for the specific rate of disappearance of triphenylmethyl chloride, $-d[RCl]/[RCl]dt$, fall progressively (Table 3). As is our practice in such cases, we deferred trying to decide the cause of this, until we had pursued the investigation further by measurement of initial specific rates, k_1°. These can always be calculated from the observations, without making any, possibly prejudicial, assumptions as to kinetic form.

A set of initial specific rates is shown in Table 1. The Table includes an illustration of the result that these first-order constants in triphenylmethyl chloride do not depend significantly on the concentration of that substance. How the constants depend on the concentration of tetra-*n*-butylammonium azide is best appreciated with the help of Fig. 1, where the logarithms of rate are plotted against the logarithms of salt concentration. We see that, as long as this concentration is below 10^{-2}M, the rate depends but little on it, but that from 10^{-2}M to 10^{-1}M the rate rises somewhat sharply, as we expected from our know-

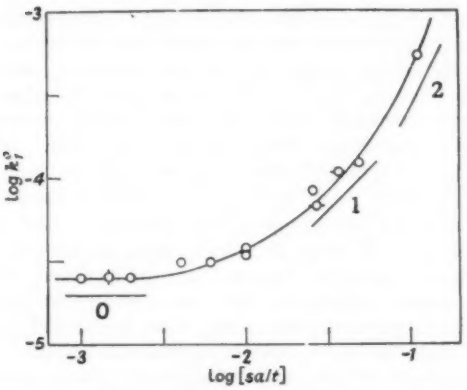

FIG. 1. *Reaction of triphenylmethyl chloride with tetra-*n*-butylammonium azide in benzene at 30°; plot of the logarithm of the initial specific rate of disappearance of triphenylmethyl chloride* versus *the logarithm of the total salt concentration*:

○ *Without any salt other than the azide.*

⊖ *With added tetra-*n*-butylammonium perchlorate.*

-○- *With added tetra-*n*-butylammonium nitrate.*

The short straight lines indicate theoretical slopes for kinetic orders of 0, 1, and 2 with respect to tetra-*n*-butylammonium azide

ledge of the electrolytic situation. Quite formally, we may say that the kinetic order of reaction with respect to salt is approximately zero below 10^{-2}M, and that it rises from just above zero to about two between 10^{-2}M and 10^{-1}M. We also notice that, in this rise, there is no obvious arrest at an order of unity, *i.e.*, the curve in Fig. 1 has no pronounced flat at unit slope.

TABLE 1. *Initial specific rates* ($k_1^\circ = \{-d[RCl]/[RCl]dt\}_0$ *in sec.*$^{-1}$) *of reaction of triphenylmethyl chloride* (RCl) *with tetra-*n*-butylammonium azide* ($M^+N_3^-$) *in benzene at* 30°.

Run	$[RCl]_0$	$[M^+N_3^-]_0$	$10^5k_1^\circ$	Run	$[RCl]_0$	$[M^+N_3^-]_0$	$10^5k_1^\circ$
412	0·02	0·0010	2·5	406	0·05	0·0100	3·4
411	,,	0·0020	2·5	221	,,	0·0250	8·5
410	,,	0·0040	3·2	220, 222, 223	,,	0·0500	12
409	,,	0·0060	3·2	225	,,	0·1120	55
407	,,	0·0100	3·8				

We may now consider how Swain and Kreevoy supported their claim that their reaction has an order of unity with respect to azide. First, they stated that second-order rate constants could be calculated from the runs; but they did not give any figures to show the actual course of a run. Secondly, they gave just three calculated second-order rate constants, which are mutually inconsistent. If we multiply these constants by the initial salt concentrations in order to get initial specific rates, k_1°, and then plot these values against the salt concentrations, as in Fig. 2, then Swain and Kreevoy's summary

of the kinetics amounts to joining these points by a straight line going through (or near) the origin. However, if it were permissible to derive any relation from only three points, it would seem more natural to join them by some curve, such as that illustrated. Moreover, regard being paid to the concentrations involved, such a curve would be generally consistent with our results, as summarised in Fig. 1. But without that comparison, and quite empirically, the three cited figures, if they indicate anything, indicate some curve, such as is shown in Fig. 2; and this curve, like our curve in Fig. 1, expresses, not an order

FIG. 2.

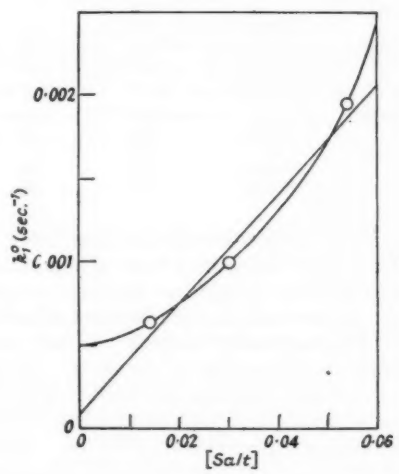

FIG. 3.

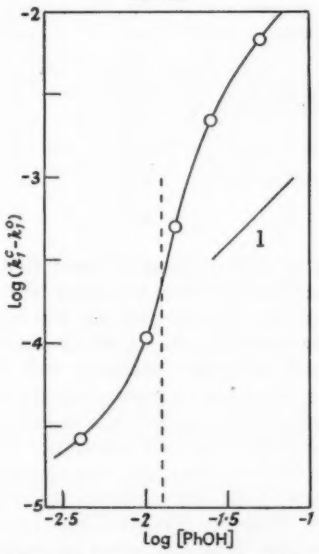

FIG. 2. *Swain and Kreevoy's data for the reaction of triphenylmethyl chloride with dimethyldi*-n-*octadecylammonium azide in benzene at* 50°; *plot of initial specific rates* versus *salt concentration.* This is the total numerical evidence given for the conclusion that the reaction is of first order in the salt. The straight line expresses this conclusion, and the curved line an alternative type of conclusion discussed in the present text.

FIG. 3. *Effect of phenol on the initial specific rates of reaction of triphenylmethyl chloride with tetra*-n-*butylammonium azide in benzene at* 30°: *plot of the logarithm of the catalysed rate against the logarithm of the concentration of phenol, other concentrations being constant.* The short line has the theoretical slope for an order of unity with respect to phenol. If only the excess of azide over phenol were kinetically effective, rates to the left of the vertical broken line would be zero.

of unity in salt, but an order rising continuously with concentration from well below unity to well above it.

Our next step was to examine the effect of added salts, the measurement still being that of initial rates. Some results are in Table 2. The only non-reacting salt we had was tetra-*n*-butylammonium perchlorate. This has no detectable kinetic effect, in the range of its solubility, which is within the range of concentration over which tetra-*n*-butylammonium azide itself has no effect on the rate. As a more soluble salt, we had available tetra-*n*-butylammonium nitrate, which probably does react with triphenylmethyl chloride, but to produce triphenylmethyl nitrate, which will subsequently, and very quickly, be converted into triphenylmethyl azide. This salt also, in its comparatively high concentration, appeared to have no more marked effect on the rate than its equivalent of extra tetra-*n*-butylammonium azide would have had. These effects are illustrated in Fig. 1.

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Significant results arose from the addition of tetra-*n*-butylammonium chloride, which depressed the initial rate at all total salt concentrations up to at least as far as 0·02M. A set of results, applying to the important dilute range, below 0·008M, is included in Table 2.

TABLE 2. *Effect of added salts* (M^+X^-) *on initial specific rates* ($k_1°$ *in sec.*$^{-1}$) *of consumption of triphenylmethyl chloride* (RCl) *by reaction with tetra*-n-*butylammonium azide* ($M^+N_3^-$) *in benzene at* 30°.

M^+X^-	Run	$[RCl]_0$	$[M^+N_3^-]_0$	$[M^+X^-]$	$10^5k_1°$ (Obs.)	$10^5k_1°$ (Calc.)
$Bu^n_4NClO_4$	412	0·02	0·0010	—	2·5	—
	417	,,	,,	0·0005	2·6	—
$Bu^n_4NNO_3$	Interpltd.	0·05	0·0125	—	3·8	—
	238	,,	,,	0·0145	6·7	—
	239	,,	,,	0·0236	11·0	—
Bu^n_4NCl	Interpltd.	0·02	0·0025	—	2·6	—
	416	,,	,,	0·0025	1·5	1·3
	410	,,	0·0040	—	3·2	—
	415	,,	,,	0·0025	2·3	2·0
	414	,,	,,	0·0040	1·4	1·6

These rate depressions show that the reaction of tetra-*n*-butylammonium azide on triphenylmethyl chloride cannot be of first order in salt, and cannot have a bimolecular mechanism. Clearly, this salt and tetra-*n*-butylammonium chloride are in sharp competition for something the supply of which is limited: the two salts are certainly not attacking any freely available substance, such as molecular triphenylmethyl chloride: if they were, neither could have a depressing effect on the initial rate of reaction of the other. We are evidently observing here the so-called "mass-law effect," first demonstrated in 1940 for the solvolytic [3] and non-solvolytic [4] substitutions of benzhydryl (diphenylmethyl) halides, and predicted at that time [5] for analogous substitutions of triphenylmethyl halides. Swain, Scott, and Lohmann subsequently observed such effects by the method of the antecedent work.[6] However, Swain has based much mechanistic speculation in part on his inability to observe the mass-law effect in reactions of triphenylmethyl chloride with hydroxylic reagents in benzene,[7] but, as will be seen also from accompanying papers, this effect has proclaimed its presence to us in every one of Swain's reactions that we have re-investigated.

There must be some ratio (called α) in which tetra-*n*-butylammonium chloride and azide concurrently attack the slowly formed intermediate. As illustrated in the last column of Table 2, the rate depressions are fairly well represented if we assume that that ratio is unity, though the errors in the determination of the initial rates are such that we should not regard this value as fixed to better than $\pm 20\%$. This means, for example, that the saline chloride, added in quantity equivalent to the azide, cuts the rate of azide substitution to one-half. However, this loss of rate does not represent the rate at which the saline chloride ion itself enters into reaction: we know the latter rate from work with radiochloride ion (Part LIV, Section 1), and it is much smaller. Yet this chloride-exchange rate is itself reduced by added saline azide according to a law of just the same form. The significance of these peculiar relations is discussed in Part LVIII (Section 2).

We can now consider the kinetic form of the reaction between triphenylmethyl chloride and tetra-*n*-butylammonium azide. The fact that the specific rate, calculated as a first-order constant in triphenylmethyl chloride, falls as reaction progresses, is obviously not to be explained by assuming that the reaction is of first order, or any other non-zero order, in the salt: the reaction does not proceed continually more slowly because this azide is

[3] Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 979.
[4] Bateman, Hughes, and Ingold, *J.*, 1940, 1017.
[5] Bateman, Hughes, and Ingold, *J.*, 1940, 960.
[6] Swain, Scott, and Lohmann, *J. Amer. Chem. Soc.*, 1953, **75**, 136; cf. also ref. 1.
[7] Swain, *J. Amer. Chem. Soc.*, 1948, **70**, 1119; 1950, **72**, 2790.

disappearing; for, when we take most of it away at the outset, the reaction does not (in the dilute range) go more slowly. The reason why the reaction slows down as it progresses is that tetra-*n*-butylammonium chloride is appearing. We are, indeed, observing once more the mass-law effect of an S_N1 reaction, and in just the form in which it was originally noticed in the S_N1 reactions of benzhydryl halides.

We can account for the progressive fall of specific rate, to within the accuracy of the measurements, on the basis of the kinetic outline,

$$RCl \underset{k_2(Cl^-)}{\overset{k_1}{\rightleftharpoons}} R^+ \xrightarrow[(N_3^-)]{k_3} RN_3$$

with $k_1 \ll k_2$, k_3, and $k_2/k_3 = \alpha$. The normal object of our kinetic experiments is to derive initial specific rates, $k_1°$, because we can do that without making any hypothesis as to mechanism. These rates are the limiting initial values (as $x \longrightarrow 0$) of first-order rate constants $k_1^{(x)}$, calculated from familiar standard formulæ, which are identical with those which would apply to the above reaction scheme in the special case $\alpha = 0$, *viz.*:

$$dx/dt = k_1^{(x)}(a - x) \qquad k_1^{(x)}t = \ln \{a/(a - x)\}$$

where a is the initial concentration of triphenylmethyl chloride. The mass-law being into account, *i.e.*, on the assumption that $\alpha \neq 0$, these equations become generalised to:

$$\frac{dx}{dt} = k_1 \frac{(a - x)(b - x)}{b - x + \alpha x} \qquad k_1 t = \left(1 - \frac{\alpha a}{a - b}\right) \ln \frac{a}{a - b} + \left(\frac{\alpha b}{a - b}\right) \ln \frac{b}{b - x}$$

where b is the initial concentration of tetra-*n*-butylammonium azide. The constant α is disposable, but is not very critical: any values from about 0·8 to 1·2 will usually give fair agreement with our data.

In illustrating the application of these equations, we have to explain that, in order to get the best possible initial specific rates from our not always very accurate analytical determinations, we habitually reduced the latter in two ways, of which the first was mainly treated as a check, whilst the second was regarded as leading to the more reliable initial rates $k_1°$. In method (1), $k_1^{(x)}$ was calculated directly from the observations, by using the integrated first-order equation, and the set of values so obtained was plotted to give $k_1°$ by extrapolation. In method (2), which was preferred, a smooth curve, giving the best (visual) fit to the observations, was drawn, and $k_1^{(x)}$ was similarly calculated for a series of points along it; and then these values were plotted, so affording $k_1°$ by extrapolation. In Table 3 we show this type of treatment for a sample run, but with the addition that, in association with each method, the constant k_1 also is calculated by means of the generalised form of the integrated equation, with α set equal to 1·2. The constants are nearly as good if we take α as 1·0.

In the preceding paper, it was shown that the chloride-exchange substitution of triphenylmethyl chloride in benzene has the most diagnostic characteristics of an S_N1 type of mechanism. We have just shown that the corresponding azide substitution also has those characteristics. These independent conclusions are based on the internal evidence derived from the study of each reaction separately. The simplest trial synthesis of the conclusions would be that obtained by supposing that both substitutions have their rate determined by one and the same slow process. However, the absolute rates show that the real situation cannot be so simple. The specific rate of chloride exchange at 30° is $0·50 \times 10^{-5}$ sec.$^{-1}$. In similarly dilute solution, the specific rate of azide substitution at 30° is $2·5 \times 10^{-5}$ sec.$^{-1}$. In each case, then, we have a substitution of triphenylmethyl chloride, which is insensitive to the concentration of the substituting agent, but is sensitive to its nature. Here we only point out this interesting fact: we shall discuss it in Part LVIII.

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(2) *Catalysis by Phenol.*—Swain and Kreevoy [1] examined the catalytic effect of phenol on the reaction between triphenylmethyl chloride and dimethyldi-*n*-octadecylammonium azide. They describe the kinetics as third-order, after account is taken of the alleged

TABLE 3. *Kinetic form of the reaction between triphenylmethyl chloride and tetra*-n-*butylammonium azide in benzene at* 30°. *Constants for a unimolecular mechanism without* ($k_1^{(x)}$) *and with* (k_1) *allowance for mass-law retardation produced by the formed chloride ion.*

[Run 406. Initially $a = [Ph_3CCl]_0 = 0{\cdot}05$, and $b = [Bu^n_4NN_3]_0 = 0{\cdot}01$M. Percentage reaction, x, is $100s/s_\infty$ with $x_\infty = 0{\cdot}01$M. Time, t, is in min. and all k's are in sec.$^{-1}$.]

Method (1)				Method (2)			
x (%)	t	$10^5k_1^{(x)}$	10^5k_1	x (%)	t	$10^5k_1^{(x)}$	10^5k_1
7·2	7	3·28	3·62	2·5	2·5	3·33	3·37
				5	5	3·33	3·42
10·8	11	3·27	3·53	10	11	3·05	3·25
				15	17	2·98	3·28
14·8	18	2·82	3·05	20	24	2·83	3·27
				25	31	2·75	3·28
22·5	27	3·00	3·33	30	38	2·72	3·32
				35	47	2·58	3·30
34·0	42	2·60	3·55	40	57	2·58	3·28
				45	69	2·28	3·22
59·0	126	1·68	2·80	50	81	2·18	3·20
$10^5k_1°$ (by extrapn.)		3·4	—	(By extrapn.)		3·4 *	—
10^5k_1 (mean)		—	3·31	(Mean)		—	3·29

* This is the figure entered in Table 1. All other figures in Tables 1, 2, and 4 are similarly derived.

formation of a remarkable type of complex between the azide and the phenol, a complex which puts its contained azide completely out of action, but makes no difference to its contained phenol, so that the kinetic equation becomes

$$\text{Rate} \propto [\text{RCl}]([\text{Azide}] - [\text{Phenol}])[\text{Phenol}]$$

the middle factor being allowed its true value only if it is positive, and being taken as zero if in fact it is negative. Their summary of their kinetic findings is presented without any numerical support whatever: one figure is given, which is said to be a mean of third-order rate constants calculated thus for three runs, to which no individual reference is made. This is the sole basis on which it is concluded that the reaction is of termolecular type (called "third-order" in this paper), and, furthermore, that a two-step mechanism, based on ionisation, and involving azide intervention in the second step, is excluded.

We have made an examination of the catalysis by phenol of the reaction between triphenylmethyl chloride and tetra-*n*-butylammonium azide. We found, as expected, no definite order with respect to phenol. Though complex-formation cannot be excluded in principle, we have found no positive indication of the formation of a complex with the properties ascribed to it by Swain and Kreevoy. Both points may be illustrated by the

TABLE 4. *Effect of added phenol on initial specific rate* ($k_1°$ *in sec.*$^{-1}$) *of consumption of triphenylmethyl chloride by reaction with tetra*-n-*butylammonium azide in benzene at* 30°.

[Initially, $[Ph_3CCl]_0 = 0{\cdot}05$M, throughout.]

Run	$[Bu_4NN_3]$	[PhOH]	$10^5k_1°$	Run	$[Bu_4NN_3]$	[PhOH]	$10^5k_1°$
Interpoln.	0·125	—	3·8	228	0·0125	0·025	225
226	,,	0·004	6·2	229	,,	0·050	670
227	,,	0·010	14·2	220, 222, 223	0·0500	—	12
231	,,	0·015	53·3	232	—	0·015	19

longer of the sets of runs shown in Table 4, where we have a constant concentration of the azide throughout, and a rising concentration of phenol from run to run. As usual, we record initial specific rates $k_1°$.

If we plot the logarithm of the excess rate due to phenol against the logarithm of the concentration of phenol, we obtain the curve shown in Fig. 3. Its slope varies continuously, showing no arrest at unity, or any other integral value within the range of the observations. If the kinetics were to be represented by Swain and Kreevoy's equation, then the rates must approximate to zero to the left of the vertical broken line in Fig. 3, where there would be no excess of azide over phenol.

With higher concentrations of tetra-*n*-butylammonium azide, the catalytic effect of phenol is generally similar but weaker. This may possibly be because, at the higher concentration of salt, higher multipolar aggregates, or more highly charged aggregates, of chemically active character, are formed by the salt, aggregates which the added phenol helps to break down, this retarding effect being superposed on the accelerating effect, which alone the phenol exerts at low concentrations of salt.

The short summary of these results on phenol catalysis is that, contrary to Swain and Kreevoy's statements, the catalysed reaction is not of third order, is not of first order in phenol, and, in fact, has no definite kinetic order in phenol. We conclude that there is no unique placing, such as is required by Swain's " push-pull " mechanism, of just one phenol molecule in the transition state of the catalysed substitution; and that the rôle of phenol is susceptible only of statistical description, as is implied in its classification as that of a co-solvent.

Experimental

Materials.—Their preparation is described in the preceding paper.

Kinetic Method.—The reaction mixtures were made up as usual (preceding paper), but to a total volume of 50 ml. Samples of 5 ml. were run into 5 ml. of redistilled aniline, which served as an efficient quenching medium, interrupting the reaction and liberating hydrogen chloride quantitatively from the triphenylmethyl chloride remaining in the sample. To this mixture, 20 ml. of 95% ethyl alcohol, containing bromothymol-blue, were added, and then a standard volume of 0·05N-sodium hydroxide in ethyl alcohol was added from an automatic pipette. This volume was 2 ml., 5 ml., or 7 ml., according as the initial concentration of triphenylmethyl chloride in the kinetic run had been 0·02, 0·05, or 0·07M. The solution was then titrated with 0·01N-hydrochloric acid in ethyl alcohol, to a colour standard. Two samples were withdrawn from each run as soon as possible after its commencement, and the mean time of withdrawal, and the mean of the analytical results obtained with the samples, were taken as defining the kinetic starting point. Formed triphenylmethyl azide was not affected by this procedure. Checks of the method were made without azide. The methods of calculation have been described, and typical results have been given, in the foregoing text.

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238. *Mechanism of Substitution at a Saturated Carbon Atom. Part LVI.* Kinetics of the Reaction of Triphenylmethyl Chloride with Methyl Alcohol in Benzene.*

By E. D. Hughes, C. K. Ingold, (Miss) S. F. Mok, and Y. Pocker.

The methyl-alcoholysis of triphenylmethyl chloride in benzene has been reinvestigated. Swain reported measurements of the rate of this reaction in the presence of pyridine, asserting that pyridine does not react with the alkyl chloride and has no effect on the rate of its alcoholysis. It has been found that pyridine reacts relatively rapidly with triphenylmethyl chloride, and has a marked effect on the rate of its methyl-alcoholysis. The present investigation was therefore continued by the measurement of initial rates in the absence of pyridine.

Contrary to Swain's finding that the kinetic order is precisely two with respect to methyl alcohol, it is now found that this reaction has no definite order in that substance: the apparent order rises quite continuously from near zero to about three over our range of methyl alcohol concentrations, without any sign of an arrest at any intermediate value. Notwithstanding that methyl alcohol is the substituting agent, it appears to be exerting a macroscopic co-solvent effect on a rate-controlling step, and no evidence is forthcoming that two necessary and sufficient molecules have specific functions in the transition state, as is required by Swain's "push-pull" theory. A similar general co-solvent function is exerted by a number of added polar molecules, which are not acting as substituting agent: those investigated include the non-reacting aprotic molecules, nitromethane and nitrobenzene, and the slowly reacting hydroxylic molecule, phenol.

Swain claimed that the rate of alcoholysis is not depressed by common-ion salts (chlorides), and is not appreciably increased by non-common-ion salts. It is found, on the contrary, that tetra-*n*-butylammonium chloride markedly depresses the reaction rate. The functional form of the effect is in approximate agreement with the assumption that this is the "common-ion" effect in a reaction of S_N1 type, *i.e.*, competitive intervention by the saline chloride in a product-controlling step, following a rate-governing step, of the reaction.

Hydrogen chloride is an electrophilic catalyst, apparently acting both through its molecules, and also through dissociated protons. Tetra-*n*-butylammonium perchlorate is a remarkably powerful catalyst, apparently acting through dissociated perchlorate ions. Other non-common-ion salts accelerate the reaction markedly, but less strongly than perchlorate: a reason for the quantitative difference is suggested. Added tetra-*n*-butylammonium chloride destroys the catalytic effect of hydrogen chloride by combining with it: protons are converted into hydrogen chloride molecules, and the latter are further converted into hydrogen-dichloride ions. Tetra-*n*-butylammonium chloride also destroys the catalytic effect of tetra-*n*-butylammonium perchlorate: the functional form of this effect is in accurate accord with the assumption that the saline chloride is again intervening, not in the first rate-controlling step, but in a product-controlling step of an S_N1-type mechanism.

Swain's conclusion [1,2] that "there is only one mechanism for the displacement of anions," "always a push-pull termolecular mechanism," that "nucleophilic displacement reactions .... are at least termolecular, never unimolecular or bimolecular," and that they have "exactly third order kinetics," unless solvent participation suppresses certain orders, inasmuch as "kinetics does not depend on mechanism, but only on the degree of

* Part LV, preceding paper.

[1] Swain, *J. Amer. Chem. Soc.*, 1948, **70**, 1119.
[2] Swain and Eddy, *ibid.*, p. 2989.

participation of the solvent," has been supported by several experimental reports, of which the most widely quoted is that on the reaction of triphenylmethyl chloride with methyl alcohol in benzene. It is claimed [1,3] that this process obeys a third-order rate law with precision, and that the positive normal, and negative, mass-law salt effects, which might be expected to appear if the unimolecular mechanism S_N1 were in operation, are insignificant or absent.

In re-examining this subject, our first object was to check the kinetic facts: we found that they were not as reported. We then continued the investigation, because it became our object to see whether a more comprehensive survey of the kinetic pattern would appear consistent with either the S_N1 or the S_N2 mechanism of substitution, the concept of which, according to Swain, " has been popular " but is to be rejected as " false and misleading." [4,5]

(1) *The Experimental Conditions.*—They were our first difficulty. Swain's main series of data relate to the reaction of triphenylmethyl chloride (0·1M) with methyl alcohol (0·05 or 0·1M), sometimes with added phenol, but always with an added tertiary amine, usually pyridine in excess (0·1—0·2M), in a benzene solution saturated with, and containing in suspension, the hydrochloride of the amine. Swain does not suppose that such conditions are either needlessly, or dangerously, over-complicated. " The amine," he writes, is used simply to take up the hydrogen chloride formed and render the reaction irreversible. The reaction between trityl chloride and tertiary amines is negligibly slow under these conditions, and the rate of reaction with methanol is unaffected by changing the concentration of the tertiary amine used."

We do not confirm either of these findings. As to the first, we find that triphenylmethyl chloride reacts rapidly with tertiary amines, in particular, with pyridine. The reaction is reversible, but it goes forward extensively, and the forward rate is comparable with the rate of chlorine exchange of triphenylmethyl chloride with a saline radiochloride. a reaction which is generally faster than methyl-alcoholysis in like conditions, *e.g.*, 8 times faster in the presence of 0·1M-methyl alcohol in benzene (Part LIV). The time element can, as indicated in Part LIV, be studied conveniently by competition with chloride exchange; but the kinetics and thermodynamics of the reaction of triphenylmethyl chloride with pyridine are the subjects of a future paper, and we are concerned now only with the qualitatively greater rapidity of this reaction than of the reaction with methyl alcohol. The result of it is that, before the progress of the reaction with methyl alcohol comes to be measured, the faster reaction with pyridine has converted a certain proportion of the triphenylmethyl chloride into a form, which is not unreactive, but is less reactive than is the original material, towards methyl alcohol. And so, contrary to Swain's second finding, we observe that the rate of methyl-alcoholysis is reduced by added pyridine, and reduced the more by an increased concentration of pyridine. This is illustrated by the initial specific rates, $k_1 = -\mathrm{d}[\mathrm{RCl}]/[\mathrm{RCl}]\mathrm{d}t$, cited in Table 1.

TABLE 1. *Effect of added pyridine on the initial specific rate (k_1 in sec.$^{-1}$) of reaction of triphenyl chloride with methyl alcohol in benzene at 25°.*

(Initially, triphenylmethyl chloride was 0·1M, throughout.)

Run	$[MeOH]_0$	[Pyridine]	10^5k_1	Run	[MeOH]	[Pyridine]	10^5k_1
146	0·10	—	6·3	219	0·05	—	2·17
16	,,	0·05	3·4	17	,,	0·10	1·09
5	,,	0·10	2·8	26	,,	0·20	0·90
33	,,	0·60	2·2	34	,,	0·60	0·67

There is a slight quantitative exaggeration in this Table, inasmuch as the pyridine-free rates are rendered too high by the catalytic effect of adventitious hydrogen chloride. We know how to correct for this: and we know that, if the correction were made, it would

[3] Swain, *J. Amer. Chem. Soc.*, 1950, **72**, 2794.
[4] Swain and Langsdorf, *ibid.*, 1951, **73**, 2813.
[5] Swain and Moseley, *ibid.*, 1955, **77**, 3727.

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not reduce the pyridine-free rates by more than 10%. This does not affect the conclusion that the rate is seriously disturbed by pyridine.

Since the findings on which Swain based the choice of his experimental conditions were not confirmed, it was evident that we could not continue to employ those conditions. A simplified procedure was required, and it was an obvious step to leave out the pyridine, and, of course, the pyridine hydrochloride, and to study initial rates. We expected that two new disturbances would arise in the continuing reaction, *viz.*, an autocatalytic acceleration, due to formed hydrogen chloride,[6] and a final retardation due to reversibility. However, by concentrating on initial rates, we could largely avoid disturbances. We soon found that a careful watch had to be kept on the effect, on initial rates, of adventitious hydrogen chloride. But this was a small problem compared with that of analysing the kinetics of two interacting, simultaneous, reversible reactions, both, as we now know, having inconstant reaction orders.

(2) *Order with Respect to Triphenylmethyl Chloride.*—In agreement with Swain,[1] we find that this kinetic order is unity. This is illustrated, in the first instance, by the initial specific rates, $-d[RCl]/[RCl]dt$, in Table 2, for two methyl alcohol concentrations. Here, the rate constants are uncorrected for catalysis by adventitious hydrogen chloride, but in these experiments the error so caused was only of the order of magnitude of the casual errors of the initial-rate measurements.

TABLE 2. *Effect of the concentration of triphenylmethyl chloride* (RCl) *on the initial specific rate* (k_1 *in sec.*$^{-1}$) *of its reaction with methyl alcohol at* 25°.

Run	$[RCl]_0$	$[MeOH]_0$	10^5k_1	Run	$[RCl]_0$	$[MeOH]_0$	10^5k_1
206	0·010	0·10	6·7	217	0·010	0·20	33
211*d*	0·020	,,	5·0	218	0·020	,,	37
207	0·025	,,	5·5	219	0·030	,,	38
212	0·030	,,	6·0	220	0·050	,,	40
146	0·100	,,	6·3	393	0·100	,,	40

The test here illustrated is for a range 1 : 10 of triphenylmethyl chloride concentrations. We have enlarged the range to 1 : 40; but, with the higher concentrations of triphenylmethyl chloride, it is more difficult to keep down the adventitious hydrogen chloride, and it is easier to allow it to enter, but to correct for it. This further illustration must therefore wait until we go into the matter of hydrogen chloride catalysis (Section 4).

In the particular experiments to which Table 2 refers, we did not measure the equilibrium extent of reaction. But this is known approximately from many other measurements: when triphenylmethyl chloride and methyl alcohol are in equivalence, the reaction goes forward to the extent of about 11%, but when either reagent is in excess over the other, then the consumption of that in deficit proceeds much further, *e.g.*, to more than 80%.

(3) *"Order" with Respect to Methyl Alcohol.*—According to Swain, the reaction between triphenylmethyl chloride and methyl alcohol, besides being of first order in triphenylmethyl chloride, is of second order in methyl alcohol, and so of third order overall, these orders holding with great accuracy: "The fact that the order is so precisely third," he says, "suggests that we are dealing with a pure mechanism, which accounts for all the reaction observed."[1]

Our data on the dependence of the rate on methyl alcohol concentration are in Table 3. The concentration range is 1 : 250, with the accuracy falling off at both extremes, but with a similar degree of accuracy over a central range of 1 : 80. The rates are again uncorrected for catalysis by adventitious hydrogen chloride, but the correction that some of the figures need on this account is not more than twice the casual error, and is of no significance in a range of rates of 1 : 1000. It happens that the equilibrium extent of reaction was measured in many of these experiments, and so we take the opportunity to illustrate this matter in Table 3.

[6] Bateman, Cooper, and Hughes, *J.*, 1940, 930 (electrophilic catalysis by HCl of alkyl chloride reactions in aprotic solvents); Part LIII, Hughes, Ingold, Patai, and Pocker, *J.*, 1957, 1206 (stability of $ClHCl^-$ ion in benzene, the reason for the catalysis).

TABLE 3. *Effect of the concentration of methyl alcohol on the initial specific rate (k_1 in sec.$^{-1}$) of its reaction with triphenylmethyl chloride* (RCl) *in benzene at* 25° ($[RCl]_0 = 0{\cdot}1$M).

Run	[MeOH]	10^5k_1	MeOH (%) *	Run	[MeOH]	10^5k_1	MeOH (%) *
250	0·002	~0·35	85·0	131	0·075	4·5	12·0
253	0·003	~0·42	60·0	146	0·100	6·3	10·5
249	0·005	0·30	42·0	130	,,	7·0	11·0
248	0·010	0·42	32·0	156	,,	7·3	11·0
132	,,	0·43	—				
410	0·020	0·65	—				RCl (%) *
370	,,	0·82	—	133	0·150	20	15·0
251	0·025	0·85	—	393	0·200	40	—
128	,,	1·00	19·5	134	0·250	83	21·5
129	0·050	2·2	15·0	432	0·300	137	—
15d	,,	2·3	14·5	10	,,	140	26·0
252	,,	2·5	—	135	0·350	200	29·0
291	,,	2·6	—	136	0·400	270	32·5
359	,,	2·6	—	137	0·500	~430	39·0

* Consumed at equilibrium.

The meaning of Table 3 is best indicated by plotting the logarithm of the first-order rate-constant in triphenylmethyl chloride against the logarithm of the concentration of methyl alcohol, as in Fig. 1. According to Swain, it should be a straight line of slope 2. The curve as drawn shows every slope from 0 to 3, and there is no arrest of gradient at 2

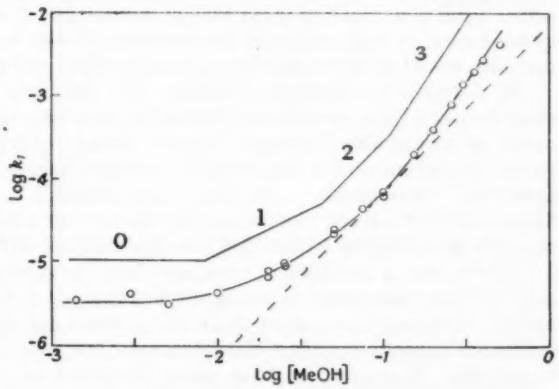

FIG. 1. *Reaction of triphenylmethyl chloride with methyl alcohol in benzene at* 25° : *plot of the logarithm of the first-order rate constant with respect to triphenylmethyl chloride against the logarithm of the concentration of methyl alcohol.*

The upper series of straight lines shows theoretical slopes for kinetic orders of 0, 1, 2, 3, with respect to methyl alcohol. The broken line represents Swain's view of the kinetics of this reaction, the kinetics required by the "push-pull termolecular" theory.

or any other integral value within the range. We cannot be quite sure that the represented arrest at 0 is real, because our experiments at low concentrations of methyl alcohol are not accurate enough.

The description given by Swain of the kinetics of this reaction is therefore incorrect in its most fundamental point. It follows that his conclusions cannot be sustained. There cannot be a small, necessary, and sufficient number, two or any other, of methyl alcohol molecules, singularly placed, with distinctive functions, in the transition state of the rate-controlling step of this reaction. Certainly, methyl alcohol is the nucleophilic substituting agent. But the kinetic evidence is that its participation in the rate-controlling stage of substitution is of the nature of that of a polar co-solvent, the molecules acting in an electrostatic way, in various numbers, from various positions, not necessarily very close to the reaction centre, and in a manner that could not be accurately described, otherwise than statistically. It follows that Swain's simple "push-pull" diagram has no sound factual basis.

Swain and Kreevoy have complained [7] that one of us "reclassified" the reaction of triphenylmethyl chloride with methyl alcohol in benzene as an S_N2 process. But that was accepting Swain's reported facts; and what was said [8] was that they allow that

[7] Swain and Kreevoy, *J. Amer. Chem. Soc.*, 1955, **77**, 1122.
[8] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell & Son, London, 1953, p. 356.

interpretation, as indeed they do. The present observations do not allow it. Hawthorne and Cram [9] have similarly disagreed with what they call "the experimentally unsupported viewpoint of Hughes" that the reaction is of S_N2 type. Actually the viewpoint was not experimentally unsupported: it was insecurely supported by Swain's experiments which we have now shown to be inaccurate. No comparison of absolute rates with Swain's values is possible because of the complications arising from the bases he added.

As this reaction has no invariable reaction-order, an activation energy, as determined from the temperature coefficient of reaction rate, would have no clear meaning. It is, however, convenient for the purpose of comparing the absolute rates of different reactions of triphenylmethyl chloride, not all of them measured at the same temperature, to have an idea of the experimental temperature coefficient of the rate of reaction with methyl alcohol. We have estimated this roughly for the methyl alcohol concentration 0·05M, by rate measurements at 25°, 35°, and 45°, and find the factor of increase for 10° rise in temperature to be close to 1·6.

Hudson and Saville [10] investigated the ethyl-alcoholysis of triphenylmethyl chloride in solvent carbon tetrachloride, in the range 0·1—5M-ethyl alcohol. Their logarithmic plot, corresponding to that of Fig. 1, showed slopes varying continuously, but non-monotonically, from below 2 to about 3. Where their concentration range and ours overlap, the slopes are not widely different, though neither is constant. They suggest that the active agent is a trimer of ethyl alcohol, but we find it difficult to believe that a probably cyclic trimer, in such relatively low concentration as would give an approximately cubic rate-law, would be more effective in reaction than the monomer.

(4) *Catalysis by Hydrogen Chloride.*—The difficulty of this subject is that there are really two catalyses, one of which would be very easy to miss. There is one of moderate power at measurable hydrogen chloride concentrations, and also one of great specific power at concentrations too small for accurate measurement. For convenience we call them the "measurable" and the "immeasurable" catalysis. The difficulty of the diagnosis is this: if one determines reaction rate for a series of concentrations of hydrogen chloride, down to the lowest that one can measure with some attempt at precision, say 5×10^{-4}M, and if one then extrapolates down to zero concentration, in order to get the acid-free rate, the answer is wrong, with nothing in the work to indicate that it might be wrong. Obviously we cannot check the acid-free rate directly, because, however early one makes one's measurements of the initial rate, one must allow a measurable amount of acid to develop. Moreover, we have never succeeded in reducing the adventitious acid in, say, a 0·1M-solution of triphenylmethyl chloride, with all manipulations made in readiness

TABLE 4. *Effect of hydrogen chloride on the initial specific rate (k_1 in sec.$^{-1}$) of reaction of triphenylmethyl chloride* (RCl) *with methyl alcohol in benzene at* 25°.

(Initially, [MeOH] = 0·1M throughout. As far as possible, the value of h = [HCl] is taken as that at the centre of the small concentration range covered by the group of initial measurements from which the initial rate was determined.)

Run	$[RCl]_0$	10^4h	10^5k_1	Equil. (%) *	Run	$[RCl]_0$	10^4h	10^5k_1	Equil. (%) *
—	—	0	7·0†	—	108	0·3	32·0	15·7	—
92	0·1	6·2	8·3	10·6	123	0·1	37·3	13·4	9·0
115	,,	14·0	10·0	10·2	112	,,	47·0	19·5	9·0
12	,,	15·0	10·3	—	110	0·4	60·0	20·7	—
106	0·2	16·0	11·7	9·5	114	0·1	87·0	25·8	8·0
122	0·1	23·3	12·7	—	121	,,	117·5	34·0	7·0

* Percentage of methyl alcohol consumed at equilibrium.
† Value by extrapolation: not the true value.

for a run, to less than an estimated 2×10^{-5}M, so that all our runs started acid, besides becoming more acid during the measurements.

The measurable catalysis is easily documented. Table 4 does this, and also takes

[9] Hawthorne and Cram, *J. Amer. Chem. Soc.*, 1954, **76**, 3451.
[10] Hudson and Saville, *J.*, 1955, 4130.

care of two further points. One, promised in Section 2, is that the reaction is of first order in triphenylmethyl chloride, not only from 0·01 to 0·10M, but also over the extension of range to 0·40M. The other is that added hydrogen chloride represses the reaction equilibrium in the direction of the factors, as would be expected qualitatively, since hydrogen chloride is a product of the reaction.

The form of the catalysis is shown in Fig. 2: it is linear: and points representing experiments with from 0·1M- to 0·4M-triphenylmethyl chloride lie about the same line. Here we have an apparently real reaction order, one of unity in hydrogen chloride. The rate term is of the form $k'h$, the catalytic coefficient k' having the value 0·023 sec.$^{-1}$ mole^{-1} l. in 0·1M-methyl alcohol in benzene at 25°; h is the concentration of hydrogen chloride.

We assume that the hydrogen chloride molecule is functioning here as a catalyst of the specific electrophilic type, discussed as to principle in 1940, and that it owes its power

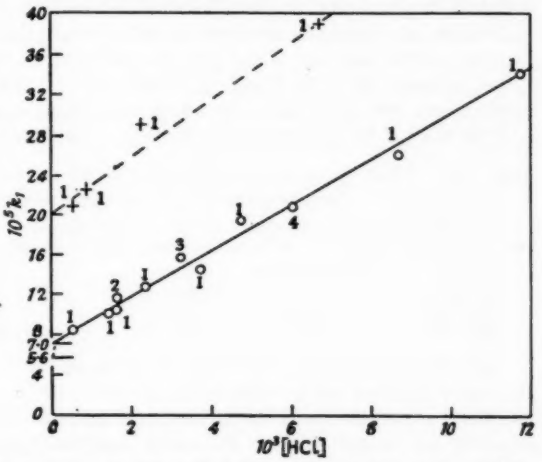

FIG. 2. *The full-line curve represents the effect of hydrogen chloride on the initial specific rate of reaction of triphenylmethyl chloride with methyl alcohol in benzene at* 25°.

According as the points are numbered 1, 2, 3, 4, the concentration of triphenylmethyl chloride was 0·1, 0·2, 0·3, 0·4M. The concentration of methyl alcohol was 0·1M throughout. The non-linear extrapolation (broken) on the extreme left of the lower (full) curve is referred to later in this Section. The linear broken curve, representing experiments in the presence of 0·001M-tetra-*n*-butylammonium perchlorate, is referred to in Section 6.

to the stability of the $(ClHCl)^-$ ion in benzene.[6] The kinetic law shows that it is specific, *i.e.*, that, unlike methyl alcohol, hydrogen chloride does accept a specific placing of a small number of its molecules, one, in fact, in the transition state of catalysed reaction.

Before we can consider the "immeasurable" catalysis, it is necessary to notice the effect of tetra-*n*-butylammonium chloride in suppressing the measurable catalysis by hydrogen chloride. We know that chloride ion combines with hydrogen chloride to give the hydrogen-dichloride ion: therefore we must expect a suppression of the catalysis. The figures in Table 5 show that a quantity of salt equivalent to the hydrogen chloride destroys

TABLE 5. *Suppression by tetra-*n*-butylammonium chloride of the catalysis by hydrogen chloride of the reaction of triphenylmethyl chloride with methyl alcohol in benzene at* 25°.

[Triphenylmethyl chloride and methyl alcohol are each in concentration 0·1M throughout. Initial specific rates k_1 are in sec.$^{-1}$.]

Run	10^4h	[Bu^n_4NCl]	10^5k_1	Run	10^4h	[Bu^n_4NCl]	10^5k_1
Fig. 2	76	—	25·5	Fig. 2	13	—	10·0
279	,,	0·0010	23·8	276	,,	0·0199	4·3
278	,,	0·0070	14·0	Fig. 2	0	—	7·0
277	,,	0·0199	4·7	275	,,	0·0199	4·3

much of the catalytic effect of the latter, and that three times as much salt more than suffices to destroy the whole of it. (Actually, at the highest concentration shown in Table 5, the salt is not only suppressing all the forms of hydrogen chloride catalysis, but is also beginning to exert its own specific power of retarding the reaction.)

Knowing that it requires an amount of tetra-*n*-butylammonium chloride in excess of the amount of hydrogen chloride to suppress nearly all the measurable catalysis of the

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latter, we can estimate about how much salt should be needed to suppress this catalysis at the lowest concentrations that can be determined, in association with a measured rate, say, 5×10^{-4}M for experiments with triphenylmethyl chloride and methyl alcohol both 0·1M. We can also estimate, from the form of this catalysis, what the rate should be in its absence. Thus, for the conditions represented by the first point in Fig. 2, we can say that the required amount of salt would be about 10^{-3}M, and that it should depress the rate to $7{\cdot}0 \times 10^{-5}$ sec.$^{-1}$. Our evidence for a second catalytic effect of hydrogen chloride, the "immeasurable" effect, is that an amount of salt 1000 times smaller depresses the rate more than that, and that rate depressions produced by such very small concentrations of salt reach their limit well below the concentrations which begin to produce a noticeable effect on the measurable catalysis.

Numerical illustration of this effect involves the difficulty of standardising, among different experiments, the smallest amount of hydrogen chloride that can be associated with what can fairly be called initial rates. With the reagents at 0·1M-concentration, and no salt present, one can, if one pays no attention to this condition, observe various initial rates between 6×10^{-5} and 9×10^{-5} sec.$^{-1}$. The most comparable collection of experiments we have involve adventitious-plus-developed acid amounting to about 5×10^{-4}M over the period of the readings. These results are summarised in Table 6.

TABLE 6. *Effect of small concentrations of tetra-*n*-butylammonium chloride on the rate of reaction of triphenylmethyl chloride with methyl alcohol in benzene at* 25°.

(Initially, $[CPh_3Cl] = [MeOH] = 0{\cdot}1$M. In the period of the readings, the hydrogen chloride concentration h averaged 5×10^{-4}M throughout. Initial specific rates, k_1, are in sec.$^{-1}$.)

Run	$10^4[Bu^n_4NCl]$	10^5k_1	Run	$10^4[Bu^n_4NCl]$	10^5k_1
92	—	8·3	223	28	5·7
296, 301	1·07	6·4	300	107	5·5
230, 299	12·3	6·0	142d, 224, 228	240	5·7

The form of this rate depression is shown in Fig. 3. The effect is all over by the time the salt concentration has amounted to $3{\cdot}0 \times 10^{-5}$M. The rate is then $5{\cdot}6 \times 10^{-5}$ sec.$^{-1}$, and there it remains until the salt concentration is increased a great deal further. Unfortunately we cannot analyse the curve mathematically, because the acid concentration cannot be specified with sufficient precision. If we could analyse it, we would hope to prove what must now be put forward as a speculation.

It has already been made clear that the linear curve in Fig. 2 ought not to be extrapolated linearly: the true curve must turn down very close to the rate axis, somewhat as indicated by the added broken curve. Now the experimentally followed, straight curve represents a rate-term $k'h$, where h is the concentration of hydrogen chloride. That the true curve turns *down* at the end of *low* concentration indicates the presence of another rate-term with a smaller exponent than unity, *i.e.*, a term representing a specifically more powerful catalysis, but one of smaller kinetic order. We assume that this order, definitely less than 1, is $\frac{1}{2}$, *i.e.*, that the new rate term is of the form $k''h^{\frac{1}{2}}$, and that it is due to electrophilic catalysis by the protons of dissociated hydrogen chloride.

From the viewpoint of dissociation to simple ions in benzene, even quaternary ammonium salts are very weak electrolytes: they are dissociated by some millionths at most to give concentrations of ions which cannot be increased much above 10^{-10}M. But however weak salts are, hydrogen chloride must be a much weaker electrolyte. Whether we assume that it is 100 times or 10,000 times weaker, it will be true that a quaternary ammonium chloride, added in considerably smaller concentration than the hydrogen chloride, will practically completely repress dissociation of the latter. We shall later illustrate the point that a chloride is needed, *i.e.*, that any quaternary ammonium salt will not act thus (Section 6).

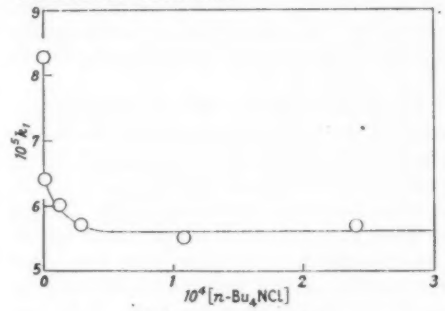
We have done similar experiments at lower methyl alcohol concentrations, down to 0·02M. The rate phenomena are of the general form shown in Fig. 3, except that the initial fall of rate is even sharper, and that at the methyl alcohol concentration 0·02M, the

horizontal stretch of curve becomes replaced by a curve with a small, but distinct, initial rise, so that it leaves a shallow minimum, and only asymptotically attains horizontality. The steepening of the initial rate fall suggests that the removal of methyl alcohol weakens hydrogen chloride, as a simple binary electrolyte, more than it weakens the quaternary ammonium salt. We have a suggestion to account for the small rise of rate, but must postpone making it until salt effects in general have been considered more thoroughly (Section 6).

(5) *Kinetic Effect of Tetra*-n-*butylammonium Chloride.*—In his first paper [1] on the reaction now under consideration, Swain reported that ammonium chlorides showed no negative kinetic effects, such as might have indicated a unimolecular mechanism S_N1: "There is no indication of a mass effect, *i.e.*, a reversal of carbonium ion formation caused by chloride ion." In a later paper be reaffirmed this finding.[3]

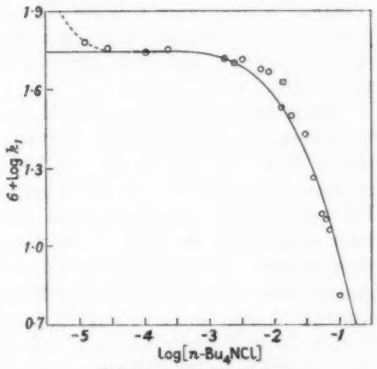
We do find a negative kinetic effect: with tetra-*n*-butylammonium chloride, it becomes noticeable at all concentrations above 10^{-3}M. By the time the added salt has become equivalent to the methyl alcohol, the rate may have fallen to one-eighth or less of its original value. This is illustrated in Table 7. The Table also shows, though in a somewhat qualitative way, that the added salt so shifts the equilibrium that the forward reaction goes further: some of the runs were followed for most of the distance they would go, and this is recorded, though the experiments were not continued for long enough to ensure that these extents of followed reaction represent equilibrium compositions.

FIG. 3. *Effect of low concentrations of tetra*-n-*butylammonium chloride on the initial specific rate of reaction of triphenylmethyl chloride with methyl alcohol at 25° in benzene.*



Each reagent is 0·1M.

FIG. 4. *Logarithmic plot showing the effect of moderate and high concentrations of tetra*-n-*butylammonium chloride on the initial specific rate of reaction of triphenylmethyl chloride with methyl alcohol in benzene at 25°.*



Each reagent is 0·1M.

TABLE 7. *Effect of moderate and large concentrations (c) of tetra*-n-*butylammonium chloride on the initial specific rate (k_1 in sec.$^{-1}$) of reaction of triphenylmethyl chloride* (0·1M) *with methyl alcohol* (0·1M) *in benzene at 25°.*

Run	10^3c	10^5k_1	Followed % *	Run	10^3c	10^5k_1	Followed % *
Section 4	—	5·6	—	148	19·0	3·17	—
150	1·77	5·2	12	152	31·3	2·67	31
14	2·50	5·0	10	149	39·6	1·83	44
145	3·41	5·2	13	153	50·9	1·32	—
144	6·81	4·8	15	154	59·6	1·27	—
151	8·80	4·7	—	157	69·7	1·15	—
143	13·6	3·4	19	158	98·1	0·65	—
147	16·5	4·3	—				

* Of the stoicheiometric maximum: the thermodynamic maxima are not much higher than the figures recorded.

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The functional form of this effect is shown in Fig. 4: in order to cover a great range of concentrations, we have made the plot one of the logarithm of the rate against the logarithm of the concentration of salt. When the salt is added in increasing amounts, the first thing it does is to destroy all catalysis by hydrogen chloride: the tail-end of that process is seen on the left. After that, nothing happens until the concentration of salt becomes a multiple percentage of that of the methyl alcohol, then the rate curve plunges downward, as seen on the right.

The curve actually drawn is not the best curve through the points, but that given by the simplest conceivably applicable form of the theory of common-ion retardation in the unimolecular mechanism S_N1. This is that the preliminary step is a rate-controlling ionisation of the alkyl halide RCl, and that the formed carbonium ion R^+, which in our case might be in the ion-pair form R^+Cl^- (we are not required to reach a decision on the point at this stage), is rapidly attacked by the added salt in ion-pair form, and by methyl alcohol, in competition. If we assume that the salt is present almost wholly as ion-pairs, that the mass-law is obeyed, and that no other kinetic effect complicates this situation, the equation representing the kinetic effect is:

$$k_1^c = k_1^0/\{(1 + \alpha c/m)\}$$

where c is the concentration of salt, m is that of methyl alcohol, k_1^c is the first-order rate-constant in the presence of the salt, and k_1^0 that in its absence, whilst α is the factor which expresses by how many times the specific rate of carbonium ion capture by salt is greater than the specific rate of its capture by methyl alcohol. In drawing the curve shown, this ratio α has been taken as 5.

Some systematic disagreement is obvious: the points near $c = 10^{-2}$ lie too high, and those near $c = 10^{-1}$ too low. Since α is adjustable, the real discrepancy might lie in only one of these regions, for we could obviously choose α to reduce either discrepancy at the expense of the other. On the other hand, the curve might be about rightly drawn as it is. For quadrupoles are likely to be less effective than ion-pairs, whilst negatively charged ionic aggregates are likely to be more effective when they can arise in more than minute proportions. From Kraus and Fuoss's work (and partly from our own), we know that quadrupoles accumulate at the expense of pairs towards $c = 10^{-2}$, and that charged higher aggregates arise in considerable quantity towards $c = 10^{-1}$. Thus our rates might well deviate from a curve which is calculated on the assumption that the salt is in a single electrolytic form by being too high near $c = 10^{-2}$ and too low near $c = 10^{-1}$, because of these known changes in the electrolytic situation with changing salt concentration.

(6) *Kinetic Effect of Other Tetra-n-butylammonium Salts, especially the Perchlorate.*—In emphasising the alleged absence, in the methyl-alcoholysis of triphenylmethyl chloride, of a mass-law retardation by adding saline chlorides, Swain remarked [1]: "It is true there is a positive salt effect, but it is of small magnitude." Actually, the few figures given do not all support this statement. However, some time later, when resisting a suggestion by Hine that, in accepting chlorides (which would be common-ion salts in an S_N1 mechanism) as suitable for testing for a positive salt-effect, Swain was taking for granted what was to be proved, the latter author examined the kinetic influence of some added tertiary ammonium sulphonates, and reported that their effect on the rate was negligible.

The over-riding objection to these experiments is that the presence of pyridine vitiates all studies of salt-effects. But even without pyridine, there would be an objection to the use of sulphonates, and it applies equally to several other classes of salt, *e.g.*, nitrates or iodides: triphenylmethyl sulphonates, nitrates, iodides, etc., probably, if not certainly, exist in covalent form. Hence the first effect of the salt might be to divert a part of the triphenylmethyl chloride from its reaction with methyl alcohol, towards reaction with the salt to give triphenylmethyl sulphonate, etc., which would subsequently enter into reaction with methyl alcohol, but at less than its normal rate, because what was intended as a non-

common-ion salt has now become a common-ion salt. Some rather complicated compensations might thus arise, resulting in a somewhat small net kinetic effect, which it would be difficult to analyse in detail until simpler cases have been adequately studied. We illustrate the sort of net effect found with salts of this general type in Table 8.

TABLE 8. *Effect of tetra*-n-*butylammonium iodide on the initial specific rate* (k_1 *in sec.*$^{-1}$) *of reactions of triphenylmethyl chloride* (0·1M) *with methyl alcohol* (0·1M) *in benzene at* 25°.

Run	[Bu^n_4NI]	10^5k_1	Run	[Bu^n_4NI]	10^5k_1
Section 4	—	5·6	163	0·001	8·3
165d	0·0001	7·5	164	0·01	10·0

We avoided these more obvious complications by using a perchlorate for detailed study. The kinetic effect of tetra-*n*-butylammonium perchlorate is not small: in 0·1M-methyl alcohol in benzene, for example, this salt, at a concentration of a few millionths molar, increases the rate by tens per cent., and at a few thousandths molar by several fold. The effect is, however, still not particularly simple: although at methyl alcohol concentrations of 0·1M and above, a very little salt shows a strong positive effect, and more salt a weaker, but still positive, one, at methyl alcohol concentrations of 0·02M and below, a small amount of salt has a negative kinetic effect, which changes to a positive effect as more salt is added. The numerical data are in Table 9, and the sort of picture they present is shown in Fig. 5.

TABLE 9. *Effect of tetra*-n-*butylammonium perchlorate on the initial specific rate* (k_1 *in sec.*$^{-1}$) *of reaction of triphenylmethyl chloride with methyl alcohol in benzene at* 25°.

[The concentration of triphenylmethyl chloride is 0·1M throughout. The various concentrations of methyl alcohol used are indicated. The concentration of salt is p (molar). The sample numbers of the salt are given, because the kinetic results themselves provide the only valid proof of adequate purity in the salt. The concentration of adventitious hydrogen chloride in the period covered by the measurements of initial rate was uniformly near 5×10^{-4}M.]

Run	Sample	10^3p	10^5k_1
[MeOH] = 0·3M:			
432	—	—	137
425, 426	5	0·007	145
427	,,	0·020	149
428	,,	0·050	155
433	,,	0·106	165
429	,,	0·200	178
430, 434	,,	0·723	201
455, 436	,,	1·60	225
[MeOH] = 0·2M:			
393	—	—	40
392	5	0·020	50
394	,,	0·050	57
395	,,	0·098	60
396	,,	0·295	75
397	,,	0·494	97
398	,,	0·995	116
400	,,	1·88	140
[MeOH] = 0·1M:			
92	—	—	8·3
265	1′	0·006	11·3
[MeOH] = 0·1M (*contd.*):			
191	1′	0·020	12·8
182b, 311	2	,,	13·2
216	1′	0·100	20·2
307, 312	2	,,	19·7
356	5	0·141	21·3
182c, 306	2	0·200	23·0
317	,,	0·453	29·5
308	,,	0·500	30·0
355	5	0·960	36·7
315	2	1·00	35·7
309	,,	1·50	40·5
318	,,	1·86	42·7
305	,,	2·00	43·3
[MeOH] = 0·05M:			
252, 291, 359	—	—	2·6
365	5	0·058	4·2
363	,,	0·094	7·5
358, 360	,,	0·240	10·4
361	,,	0·608	12·2
[MeOH] = 0·05M (*contd.*):			
362	5	1·57	16·7
364	,,	2·06	17·5
331, 333	2	2·50	18·5
[MeOH] = 0·02M:			
370	—	—	0·82
349	5	0·082	0·72
350	,,	0·234	0·69
348	,,	0·445	0·83
351	,,	0·690	1·83
357	,,	1·12	2·68
352	,,	1·60	3·07
354	,,	2·55	3·92
[MeOH] = 0·01M:			
248	—	—	0·43
367	5	0·096	0·23
368	,,	0·199	0·12
369	,,	0·330	0·65
329	2	2·50	2·08

Before we can begin to discuss these relations quantitatively, we must know what to take as the salt-free rate, and this involves investigating the relation between the kinetic effect of the salt, and that of hydrogen chloride, since a little of the latter is always present during the measurements. We had this problem in our study of the kinetic effect of tetra-*n*-butylammonium chloride: here the salt destroys the hydrogen chloride catalysis, and hence the appropriate salt-free rate was not the measured rate with salt omitted, but was the hydrogen-chloride-free rate, as determined by measurement in the presence of a very little salt. The case of tetra-*n*-butylammonium perchlorate is different: at the higher

methyl alcohol concentrations, catalyses by the salt and by hydrogen chloride are independent, and in a rough sense additive. This is illustrated by the rates in Table 10*A*, which apply to a fixed salt concentration with various amounts of adventitious-plus-introduced hydrogen chloride. Plotted in Fig. 2, these points lie about a linear curve nearly parallel to the salt-free curve for catalysis by hydrogen chloride, and displaced above it by nearly the rate-increase due to the salt in hydrogen-chloride-free conditions. At low methyl alcohol concentrations, there is an interaction between the two catalyses, as illustrated in Table 10*B*, to which we shall refer later. But our first object will be to

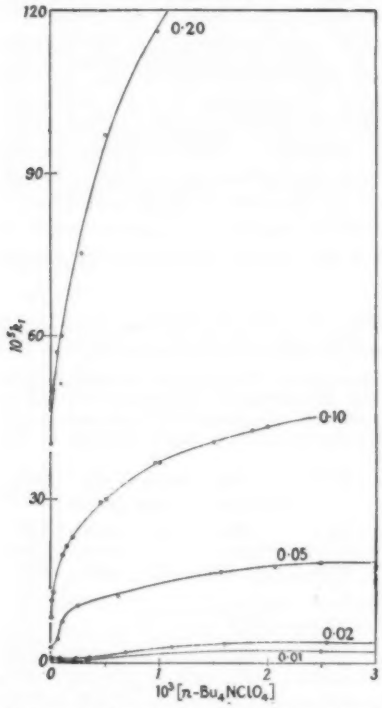


FIG. 5. *Effect of tetra-*n*-butylammonium perchlorate (in concentration p) on the initial specific rate (k_1) of reaction of triphenylmethyl chloride on methyl alcohol in benzene at 25°.*

The concentration of triphenylmethyl chloride was 0·1M throughout. The concentrations (M) of methyl alcohol are indicated by the figures against the curves.

interpret the obviously simpler situation applying to the higher methyl alcohol concentrations, and for this purpose it is clear that the salt-free rate must be taken as the directly determined rate without the salt, even though this rate includes a small catalytic contribution from the hydrogen chloride.

In order to extract a meaning from the relations illustrated in Fig. 5, we replot them as far as possible in the form log ($k_1^p - k_1^0$) *versus* log p, where k_1^p is the specific rate in the presence of a concentration p of salt, and k_1^0 is the salt-free rate discussed above. We can do this for those curves for which $k_1^p - k_1^0$ is everywhere positive, *i.e.*, for the methyl alcohol concentrations 0·3, 0·2, 0·1, and 0·05M. The result is in Fig. 6. There, the straight lines are all drawn to have a slope of $\frac{1}{2}$. We see that, for 0·3M-, 0·2M-, and 0·1M-methyl alcohol, the data agree with these lines over long ranges, though the experiments with 0·1M-methyl alcohol show diminished catalysis at the high-concentration end of the full experimental range, and the experiments with 0·05M-methyl alcohol agree with the drawn line in only a very imperfect way, inasmuch as there is reduced catalysis at both ends of the experimental range.

This is a central point in our interpretation of tetra-*n*-butylammonium perchlorate *catalysis*, as we prefer to call it, since the term " salt effect " has been so much linked with

TABLE 10. *Joint catalysis by tetra-*n*-butylammonium perchlorate and hydrogen chloride of the reaction of triphenylmethyl chloride with methyl alcohol in benzene at 25°.*

(*A*) [Triphenylmethyl chloride and methyl alcohol each 0·1M, and tetra-*n*-butylammonium perchlorate 0·001M, throughout. Initial specific rates k_1 are in sec.$^{-1}$.]

Run	HCl	10^5k_1	Run	HCl	10^5k_1
271	0·0005	20·8	273	0·0023	27·0
272	0·0008	22·5	274	0·0067	39·2

(*B*) [In the following runs, triphenylmethyl chloride is 0·1M, methyl alcohol 0·02M, and hydrogen chloride 0·001M; the concentration of tetra-*n*-butylammonium perchlorate is varied. For comparison, interpolated values from Table 9 are given, corresponding to the hydrogen chloride concentration 0·0005M, all other concentrations being the same. Initial specific rates k_1 are in sec.$^{-1}$.]

Run	$[Bu^n_4NClO_4]$	10^5k_1 (HCl = 0·001M)	10^5k_1 (HCl = 0·0005M)	$\Delta(10^5k_1)$ for ΔHCl = 0·0005M
415	—	1·0	0·8	0·2
418	0·00074	2·5	2·2	0·3
419	0·00174	7·0	3·3	3·7
420	0·00262	8·2	4·0	4·2

the ionic-atmosphere concept, which is inapplicable to solvent benzene: we have found that the catalysis has a limiting kinetic order of ½. This kinetic "square-root law" is better obeyed in the higher methyl alcohol concentrations, but even there it is not generally obeyed for salt concentrations above 10^{-3}M. Now we know that at all concentrations up to 10^{-3}M, but not necessarily much above that value, nearly all the salt is present as ion-pairs. Therefore the evident meaning of our square-root relation is that one simple ion only of the salt is involved in the transition state of the reaction. We can go further and say that ion-pairs as such are not involved, even though they are so plentiful, nor are higher aggregates, over the range in which the square-root law is obeyed. Because different tetra-*n*-butylammonium salts behave so differently, there can be no doubt that the one simple ion of the perchlorate which is active is the perchlorate ion, not the tetra-*n*-butylammonium ion.

The kinetic deviations found at high salt concentrations may be ascribed to the considerable formation of higher aggregates than ion-pairs: for example, if, in the presence of such aggregates, the one active species were still the simple perchlorate ion, then the slope of the logarithmic plot should, as pairs became replaced by quadrupoles, fall from ½ to ¼. This type of deviation seems not to set in quite so early at the highest methyl alcohol concentrations used, and it may be that, in these concentrations, the methyl alcohol is beginning to be effective in resisting the formation of ionic aggregates higher than pairs.

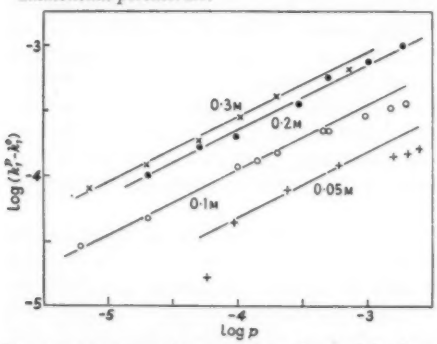
There remain for consideration the deviations which arise when the methyl alcohol concentration and the salt concentration are both low. These effects, which are retarding, first become quantitatively apparent at the methyl alcohol concentration 0·05M. They develop into a qualitatively noticeable negative catalysis at the still lower methyl alcohol concentrations 0·02M and 0·01M. As the salt concentration is built up, all these anti-catalytic tendencies or effects disappear, giving place to the usual positive catalysis.

In order to understand this, we must go back to the two hydrogen chloride catalyses, and, in particular, to what we called the "immeasurable" catalysis, which could be destroyed with very minute amounts of an ammonium chloride. Our interpretation was that this catalysis was due to simple protons, extremely active, but present in very small concentrations, so that they could be destroyed by very small amounts of a saline chloride. The basic reason why they could be so destroyed is because hydrogen chloride is a very weak acid in the benzene media, and, in particular, is weaker as an acid than the saline chloride is weak as a salt (weak though that is). A simple extension of this interpretation will allow us to understand all the low-concentration kinetic effects described above. What we have to assume is that, whilst in 0·3M-, 0·2M-, and 0·1M-methyl alcohol in benzene, perchloric acid is too strong an acid to allow an added saline perchlorate to take up the free protons, in 0·05M-methyl alcohol, it is not quite strong enough to confer on protons

so complete an immunity against the salt, and in 0·02M- and 0·01M-methyl alcohol it has become so weak as an acid, relatively to the weakness of the saline perchlorate as a salt, that a moderate amount of the saline perchlorate (though more than would have been needed of a chloride) is able to take up the free protons. This is the first effect that we observe on adding tetra-*n*-butylammonium perchlorate progressively at these low methyl alcohol concentrations: it amounts to a destruction of the "immeasurable" (protonic) part of the hydrogen chloride catalysis. A saline perchlorate cannot destroy the measurable (molecular) part of the hydrogen chloride catalysis, because the anion $ClHClO_4^-$ does not exist (Part LIII). Therefore, once the "immeasurable" acid catalysis has been dealt with, the salt becomes free to exert its own catalytic effect.

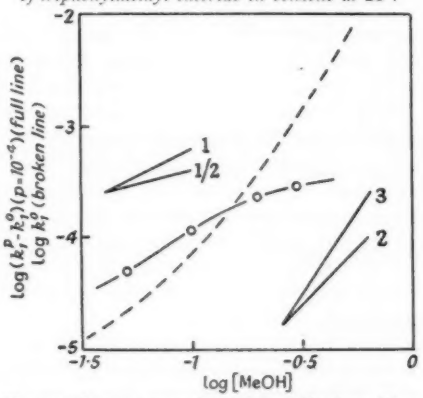
We can summarise this explanation by saying that, whilst at high methyl alcohol

FIG. 6. *Plot of logarithm of the catalysed rate of reaction of triphenylmethyl chloride with methyl alcohol in benzene at 25° against the logarithm of the concentration of the catalyst, tetra-n-butylammonium perchlorate.*



The straight lines, drawn with a slope of ½, show that this catalysis has a limiting kinetic order of ½ with respect to the salt. The different lines, each with its set of points, relate to the different methyl alcohol concentrations (M) entered against the lines.

FIG. 7. *Effect of methyl alcohol concentration on the rate of perchlorate-catalysed methyl-alcoholysis of triphenylmethyl chloride in benzene at 25°.*



The continuous curve is a plot of the logarithm of the excess rate, given by the addition of a constant concentration (10^{-5}M) of tetra-*n*-butylammonium perchlorate, *versus* the logarithm of the concentration of methyl alcohol. The broken curve is a corresponding plot for the rate of reaction in the absence of the salt. The catalysed reaction is evidently less kinetically sensitive to methyl alcohol, than is the uncatalysed reaction. The short straight lines show the slopes which would represent various simple kinetic orders in methyl alcohol.

concentrations, perchlorate catalysis is non-interacting with hydrogen chloride catalysis, at low concentrations of methyl alcohol, the perchlorate and hydrogen chloride catalyses interact. That there is a general interaction between the two forms of catalysis at low concentrations of methyl alcohol, has already been illustrated in Table 10*B*.

We can now make the suggestion which is needed to complete our interpretation of the rate curves obtained for the progressive addition of tetra-*n*-butylammonium chloride (Sections 4 and 5). What was left incomplete was the explanation of an extra feature which these curves show at low methyl alcohol concentrations. We then observe, as the salt is progressively added, first, a sharp fall of rate (destruction of both forms of hydrogen chloride catalysis), then a small rise (the unexplained additional feature), then no effect (horizontal stretch of curve), and finally a strong fall (common-ion retardation). We think that the small rise is due to catalysis by the $ClHCl^-$ ion, produced by addition of chloride ion to the adventitious hydrogen chloride. This ion must be the anion of a very strong acid (since H_2Cl_2 seems not to exist as such), and, in media in which the anion is

stable enough not to come to pieces in the process, it might act like a perchlorate ion in the transition state of the reaction under consideration. We are here assuming that the anion, which is stable in benzene but unstable in water, becomes more stable as we remove hydroxylic material, such as methyl alcohol, from the benzene solution.

Our data, and in particular the representation given in Fig. 6, provide a basis for considering the effect of methyl alcohol concentration on the rate of perchlorate-catalysed methyl-alcoholysis. If we draw a vertical line anywhere in Fig. 6, within the range of salt concentration in which the square-root law is obeyed, say, at $p = 10^{-4}$M, the catalysed rates, that can be read off from the produced intersections, may be plotted against the relevant concentrations of methyl alcohol. By " catalysed rate," we mean, of course, the excess of the total rate over what the rate would be were the salt omitted. This plot is given in Fig. 7 as a graph of the logarithm of the catalysed rate *versus* the logarithm of the methyl alcohol concentration. If we should take a different perchlorate concentration, still within the range of validity of the square-root law, the curve in Fig. 7 would simply be shifted vertically. Thus the gradient of this curve at any point represents the formal kinetic order of the catalysed reaction with respect to methyl alcohol at that concentration of methyl alcohol. One sees that, as for salt-free methyl-alcoholysis, the kinetic order in methyl alcohol of the catalysed reaction is indefinite. It is also somewhat small, varying between about one-half and one. For comparison, the analogous logarithmic plot for the uncatalysed reaction is reproduced in Fig. 7. In this, the formal kinetic order in methyl alcohol runs between about two and three. It thus appears that, in the range of perchlorate concentration over which the square-root relation holds, the catalysed reaction is less sensitive to methyl alcohol concentration than is the uncatalysed reaction. We think that this difference is of significance in connexion with the mechanism of catalysis by tetra-*n*-butylammonium perchlorate, a subject which will be discussed in Part LVIII.

(7) *Kinetic Effect of Nitromethane and Nitrobenzene.*—Since tetra-*n*-butylammonium perchlorate ion-pairs, which have a dipole moment of 14 D in benzene,[11] exert no noticeable catalytic effect at concentrations somewhat above 10^{-3}M, it is not to be expected that polar aprotic molecules, such as nitro-compounds, which have much smaller moments, and no special situation of charge distribution, such as is present in hydroxy-compounds, will exert appreciable effects except at concentrations above 10^{-2}. Actually the kinetic effects of nitromethane and nitrobenzene become marked only at concentrations of 10^{-1}M upward. Some figures are given in Table 11.

TABLE 11. *Effects of nitro-compounds on the initial specific rates (k_1 in sec.$^{-1}$) of reactions of triphenylmethyl chloride* (0·1M) *with methyl alcohol* (0·1M) *in benzene at* 25°.

Run	[$MeNO_2$]	10^5k_1	Run	[$PhNO_2$]	10^5k_1
Section 4	—	5·6	Section 4	—	5·6
76, 79, 81	0·10	7·5	82 d	0·10	7·3
78, 80 d	0·30	9·6	83 d	0·30	9·3
77	0·50	16·5	90 d	0·68	20
93 d	0·92	35	85 d	0·97	27
95 d	1·85	65	91 d	1·46	44

If we plot these rates against the concentration of the nitro-compounds we find that they lie on steepening curves. The catalysed reaction therefore has no definite kinetic order with respect to nitro-compound. The most conservative estimate that we can make of the range of variation of the formal " order " is that obtained by assuming, as is done in Table 11, that the nitro-compounds are basic enough to annul catalysis by the relatively trifling amount of adventitious hydrogen chloride, and that, accordingly, the catalysed rate is to be taken as the excess over the hydrogen-chloride-free rate, as evaluated in Section 4. If now we plot the logarithm of this excess rate against the logarithm of the concentration of nitro-compound, we get similar curved graphs, each indicating a formal kinetic order running from well below 1·0 to about 1·5 or somewhat above, over the range of the

[11] Luder, Kraus, Kraus, and Fuoss, *J. Amer. Chem. Soc.*, 1936, **58**, 225.

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data. The change in formal order would be greater if the nitro-compounds were not basic enough to behave as suggested.

We conclude that we are dealing, not with a specific "push" or "pull" of some precisely placed nitro-molecule, but with a co-solvent effect, which depends on penetrating Coulombic forces, and could not be described otherwise than in statistical terms.

(8) *Kinetic Effect of Phenol.*—This accelerating effect is strong at concentrations of phenol from 10^{-2}M upward. Some illustrative results are in Table 12. We take the

TABLE 12. *Effect of phenol on the initial specific rate (k_1 in sec.$^{-1}$) of reaction of triphenylmethyl chloride* (0·1M) *in methyl alcohol* (0·05M) *in benzene at* 25°.

Run	[PhOH]	10^5k_1	Run	[PhOH]	10^5k_1
252, 291, 359	—	2·6	406	0·0427	41·3
404	0·0107	11·7	408	0·0640	62·5
405	0·0213	21·5	409	0·0980	108

phenol-free rate as its actual experimental value, including the small catalysis by adventitious hydrogen chloride, because methyl alcohol does not annul this, and therefore it can be taken as certain that phenol will not do so.

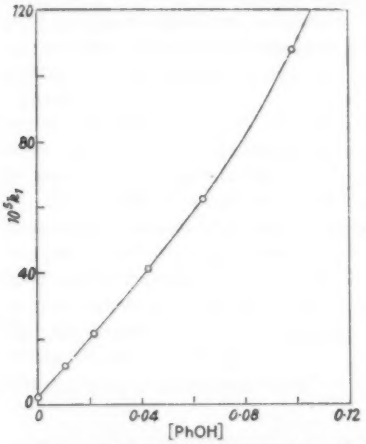

FIG. 8. *Effect of phenol on the initial specific rate of reaction of triphenylmethyl chloride* (0·1M) *with methyl alcohol* (0·05M) *in benzene at* 25°.

This catalysis was investigated by Swain,[1] who reported that the reaction was of "first order in trityl chloride, first order in methanol . . . also first order in phenol, hence again exactly third order overall." However, Swain records the use in this reaction of only two concentrations of phenol; and had we confined our observations to so few concentrations, or to such a narrow range, we also might have thought (very tentatively) that the reaction was in principle of first order in phenol. Actually the tabulated observations, covering a 9-fold concentration range, as well as other series which we could cite, lie on a nearly straight, but actually slowly steepening, curve, as shown in Fig. 8. As will appear in the next paper, when we change the reaction from methyl-alcoholysis to benzyl-alcoholysis, the rate curve, corresponding to that in Fig. 8, steepens more sharply, retaining its curvature, indicative of an inconstant, fractional, kinetic order, greater than unity, down to as low concentrations and catalytic effects as can be measured with accuracy.

(9) *Modifications produced in the Kinetic Effect of Tetra-*n*-butylammonium Perchlorate by Other Added Substances, especially Tetra-*n*-butylammonium Chloride.*—The strong accelerating effect of tetra-*n*-butylammonium perchlorate on the methyl-alcoholysis of triphenylmethyl chloride in benzene is very easily quenched by various added substances. Tetra-*n*-butylammonium chloride, which retards reaction in the absence of the perchlorate, quenches the perchlorate catalysis much more strongly: chloride equivalent to a few units

per cent. of the perchlorate is sufficient to destroy most of the catalytic effect of the latter. Other saline chlorides, such as tetraethylammonium chloride and tri-*n*-butylammonium chloride, act in a qualitatively similar way. Tetra-*n*-butylammonium iodide accelerates the methyl-alcoholysis in the absence of the perchlorate, but it still suppresses the catalytic effect of the perchlorate, in much the same qualitative way as any of the saline chlorides. The tertiary bases, pyridine and tri-*n*-butylamine, also suppress the catalysis of perchlorate. All these effects are illustrated in Table 13.

TABLE 13. *Effect of added substances* (X) *on the initial specific rate* (k_1 *in sec.*$^{-1}$) *of reaction of triphenylmethyl chloride* (0·1M) *with methyl alcohol* (0·1M) *under catalysis by tetra*-n-*butylammonium perchlorate* (P) *in benzene at* 25°.

Run	10^3[P]	10^3[X]	10^5k_1
X = *Tetra*-n-*butylammonium chloride.*			
318	1·86	—	42·7
328	,,	0·0039	33·3
326	,,	0·0065	29·2
329	,,	0·0078	27·5
325	,,	0·013	22·5
323	,,	0·026	16·5
327	,,	0·065	10·3
322	,,	0·13	8·3
320	,,	0·65	6·2
216	0·10	—	20·2
225	,,	0·0028	8·4
231	,,	0·0057	6·7
X = *Tetraethylammonium chloride.*			
216	0·10	—	20·2
256	,,	0·0061	17·8
269	,,	,,	17·4
261	,,	0·039	6·9
257	,,	0·10	6·5
X = *Tri*-n-*butylammonium chloride.*			
216	0·10	—	20·2
267	,,	0·0029	19·5
264	,,	0·0058	14·0
263	,,	0·012	10·8
215	,,	0·029	9·5
X = *Tetra*-n-*butylammonium iodide.*			
182 c, 306	0·20	—	23·0
—	,,	0·020	9·0
—	,,	1·00	8·0
216	0·10	—	20·2
283	,,	0·010	11·0
282	,,	0·100	9·3
X = *Pyridine.*			
305	2·00	—	43·3
37	,,	100·0	5·0
X = *Tri*-n-*butylamine.*			
216	0·10	—	20·2
281	,,	0·011	14·3
280	,,	0·11	8·8

There is no doubt that, among these added substances, tetra-*n*-butylammonium iodide and the two tertiary amines themselves displace chlorine from triphenylmethyl chloride. Until the kinetics of these displacements, as well as the kinetics of the subsequent changes undergone by their products in the presence of methyl alcohol, and, in particular, the kinetic effects of tetra-*n*-butylammonium perchlorate on all these processes, have been separately studied, it would be absurd to try to analyse the overall effects here under observation; and we have not attempted it. The one case, in which we could reasonably hope to solve the problem of the kinetic functional form of the quenching, is that of quenching by saline chlorides; and the simplest chloride to consider in association with tetra-*n*-butylammonium perchlorate is obviously tetra-*n*-butylammonium chloride, since, by the use of identical cations, we avoid uncertainties of cation exchange between the saline ion-pairs. For this case, the series of runs nos. 318—329, at the head of Table 12, provide suitable numerical material.

When these data are plotted, they show a rate curve, which, as the concentration of saline chloride is increased, falls towards an asymptote at or near to the uncatalysed specific rate, determined in Section 4 as $5{\cdot}6 \times 10^{-5}$ sec.$^{-1}$. The amounts of saline chloride required to produce this fall of rate lie in the range 10^{-6}—10^{-3}M; and, as the amount present when the uncatalysed rate is nearly reached is still less than 10^{-3}M, and so is too little to produce that suppression of the uncatalysed rate which is discussed in Section 5, we can evidently treat the uncatalysed and the perchlorate-catalysed rates as additive, and take the former rate term as a constant over the range of salt concentrations considered. Thus the perchlorate-catalysed rate is simply the excess of the observed rate over $5{\cdot}6 \times 10^{-5}$ sec.$^{-1}$, throughout the concentration range.

Now there are two broad ways in which a saline chloride could be imagined to reduce the perchlorate-catalysed rate. The perchlorate itself obviously intervenes in a step which is rate-influencing for the catalysed reaction: the saline chloride might interfere with that, by withdrawing perchlorate ion. Alternatively, if the reaction has a product-controlling step, in which potential substituting agents compete for a slowly produced

intermediate, the saline chloride might intervene there, and so determine a reversion to triphenylmethyl chloride. Had we not had for reference our conductance results for mixed salts (Part LIII), we should have considered the first of these possibilities very seriously: the ion-pair chloride might conceivably have withdrawn perchlorate ions to give stable, but catalytically ineffective, mixed triple anions. However, the conductance studies show that that cannot be the cause, not even a contributing cause of any importance, of the very sensitive counter-catalytic effect here under discussion: our triple-ion stability constants show that, if perchlorate ion is not withdrawn by a relatively large amount of perchlorate ion-pair, it will not be withdrawn by a much smaller amount of chloride ion-pair.

Therefore we turn to the second possibility, which is that the saline chloride enters into competition for an intermediate in limited supply. So far as concerns the determination of the eventual product, such a competition must be with methyl alcohol; but so far as concerns the catalysed rate, the competition is not necessarily with methyl alcohol

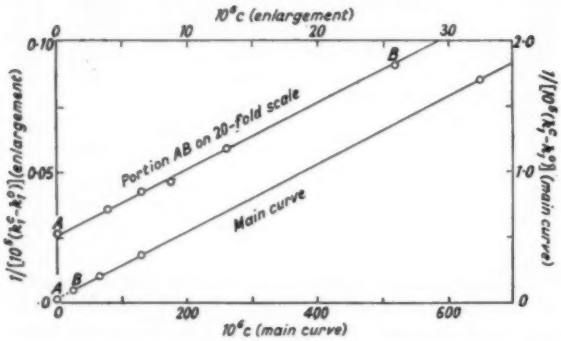

FIG. 9. *Suppression by tetra-n-butylammonium chloride of catalysis by tetra-n-butylammonium perchlorate* (0·00186M) *of the reaction of triphenylmethyl chloride* (0·1M) *with methyl alcohol* (0·1M) *in benzene at* 25°.

Plot of the reciprocal of the catalysed part of the specific rate against the concentration of the rate-suppressing agent. The initial part of the main curve contains more points than can be entered clearly, and is therefore shown separately on an enlarged scale.

alone, since the perchlorate ion itself may co-operate with one of the competitors. Other variants of this general type of mechanism can arise, according to whether the chloride enters the competition as a simple chloride ion, or as an ion-pair, or as a triple anion, and so on. This latter group of variants can be distinguished by the data for runs 318—329, in which, although the concentrations of perchlorate and methyl alcohol were kept constant, the concentration of the saline chloride was varied over a 167-fold range. The variant which best fits the data is that the saline chloride competes as its ion-pair.

The mass-law equation for rate in these circumstances is

$$k_1^{pc} - k_1^{00} = \frac{k_1^{p0} - k_1^{00}}{1 + \rho c}$$

where k_1^{pc} is the specific rate in the presence of the saline perchlorate in concentration p, and the saline chloride in concentration c, whilst ρ expresses by what factor the specific rate of capture of the intermediate by the saline chloride ion-pair is greater than the rate (not specific rate) of its capture by the other competitors. This equation assumes that practically the whole of the saline chloride is present as ion-pairs; and certainly, at the salt concentrations here employed, this condition is well fulfilled, so that we should expect a satisfactory numerical agreement.

For the series of runs 318—329, $k_1^{p0} = 42{\cdot}7 \times 10^{-5}$ sec.$^{-1}$; as shown in Section 4, k_1^{00} is $5{\cdot}6 \times 10^{-5}$ sec.$^{-1}$. The dependent variable in the above equation is k_1^{pc}, and the independent variable is c. The test for intervention of the saline chloride by competition, the actual competitor being the ion-pair, is thus to plot $1/(k_1^{pc} - k_1^{00})$ against c: this should give a straight line of slope ρ. As will be seen from Fig. 9, this law is very well obeyed. The slope of the line gives $\rho = 95500$ l. mol.$^{-1}$.

There is thus a competition for a slowly formed intermediate, and one of the

competitors, that which causes reversion to triphenylmethyl chloride, is tetra-*n*-butylammonium chloride, very probably in ion-pair form. Its opponent in the competition, that which leads to the alcoholysis products, must contain methyl alcohol, and it seems qualitatively obvious that it must also involve the perchlorate, though we have not proved this formally. This appears to follow, partly from the large value of ρ, which suggests that some essential part of the opponent must be in low concentration; and partly from the fact that the last few figures in the first section of Table 13, although they are not suitable for quantitative treatment, do indicate that, with a smaller concentration of perchlorate, ρ takes on a still larger value.

It will not be overlooked that two conclusions have been drawn about perchlorate which obviously present a problem in reconciliation. The salt is a catalyst: therefore it must be intervening *in* a rate-controlling process, since it is providing a by-pass to a process which would be rate-controlling in its absence. But, when a second substituting agent is provided, the salt also appears to be involved in a product-controlling competition for some slowly supplied intermediate: therefore it must be intervening *after* the completion of an earlier slow step. This dilemma cannot be resolved on the internal evidence of this paper; but we shall set it beside the special problems presented by the kinetic investigations of the accompanying papers, and attempt to resolve them all in Part LVIII.

Experimental

Materials.—Their preparation and purification is described in Part LIV.

Methods.—Calculated volumes of benzene solutions of all the materials to be used in a run were measured at 25°, and mixed in a 50 ml. flask, the triphenylmethyl chloride solution being introduced last. A 5 ml. sample was at once withdrawn, and run into 30 ml. of acetone at −80°: it was then titrated with a solution of triethylamine in benzene to a bromophenol blue indicator. Other samples, withdrawn after various intervals, were treated similarly. Various concentrations of standard triethylamine were used, ranging from 0·001M to 0·05M.

Results.—The essential results have already been summarised. The details given in Table 14 of illustrative runs are intended to show the commonly observed rise of specific rate, owing to autocatalysis by hydrogen chloride, succeeded, if the run is followed far enough, by a fall,

Table 14. *Illustrations of the kinetic course of the reaction of triphenylmethyl chloride with methyl alcohol in benzene at 25°.*

Run 130: Initially, $[Ph_3CCl] = 0·1$M, $[MeOH] = 0·1$M.			Run 132: Initially, $[Ph_3CCl] = 0·1$M, $[MeOH] = 0·01$M.			Run 149: Initially, $[Ph_3CCl] = 0·1$M, $[MeOH] = 0·1$M, $[n\text{-}Bu_4NCl] = 0·0396$M.		
t in min.; k_1 in sec.$^{-1}$.	% Reac. = % MeOH reacted.							
t	% Reac.	10^5k_1	t	% Reac.	10^5k_1	t	% Reac.	10^4k_1
0	0·39	—	0	2·04	—	0	0·297	—
0·5	0·60	7·0	0·5	2·18	0·46	0·5	0·350	1·77
1	0·85	7·6	1	2·32	0·42	1	0·410	1·92
2	1·45	9·0	2	2·54	0·40	2	0·520	1·87
3	2·00	9·8	5	3·32	0·42	5	0·885	1·98
5	3·30	10·3	10	4·40	0·39	10	1·51	2·18
10	7·20	11·8	15	5·44	0·38	15	2·13	2·25
15	10·5	11·8	30	9·50	0·41	40	5·30	2·15
30	11·0	6·2						

owing to reversibility. The autocatalytic rise may be reduced or may disappear, if the methyl alcohol is so reduced that only small concentrations of hydrogen chloride are formed in the measured part of the run; and again, it is reduced if tetra-*n*-butylammonium chloride is present in quantity comparable to the hydrogen chloride formed in the measured reaction. Constants k_1 are calculated from the usual first-order kinetic equation, $k_1 = (1/t)\ \ln\{a/(a - x)\}$

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239. *Mechanism of Substitution at a Saturated Carbon Atom. Part LVII.* Kinetics of the Reaction of Triphenylmethyl Chloride with Benzyl Alcohol in Benzene.*

By E. D. Hughes, C. K. Ingold, S. Patai, and Y. Pocker.

The work of Hawthorne and Cram on the benzyl-alcoholysis of triphenylmethyl chloride in benzene has been revised. It has been found that the reaction is of first order in triphenylmethyl chloride, and that, contrary to the previous authors' conclusions, it is of no particular order in benzyl alcohol, and neither is it, when phenol is present, of any particular order in phenol. In the rate-controlling stage of the alcoholysis, these hydroxy-compounds, even the alcohol which will eventually react, appear to function kinetically only as polar co-solvents, as also do polar substances which could not react, such as nitromethane and nitrobenzene.

Hydrogen chloride catalyses the alcoholysis. Tetra-*n*-butylammonium chloride retards it, first, by suppressing any catalysis or autocatalysis due to hydrogen chloride and, secondly, by a retarding mechanism of its own. Tetra-*n*-butylammonium perchlorate strongly accelerates the alcoholysis, and the corresponding nitrate produces a much milder acceleration. The catalytic effect of the perchlorate is suppressed by added nitrate, and is suppressed much more strongly by tetra-*n*-butylammonium chloride.

From these results, and in the light of the preceding paper, it is concluded that the alcoholysis is a reaction of S_N1 type, starting with a slow and rate-controlling step, in which the alcohol does not yet undergo any change, and continuing with a fast and product-controlling reaction between the carbonium ion, which is the product of the first step, and the alcohol. A saline chloride depresses the uncatalysed rate by competitively intervening in the product-controlling step. A saline chloride destroys catalysis by hydrogen chloride by combining with the catalyst. It suppresses catalysis by a saline perchlorate by competing for a slowly produced intermediate. The kinetic effects of tetra-*n*-butylammonium nitrate are probably complicated by reversible conversion of the triphenylmethyl chloride into triphenylmethyl nitrate.

The " push-pull " mechanism of Swain has no place in this picture, and is, indeed, excluded by the results.

Swain claimed that nucleophilic substitutions, not only of triphenylmethyl chloride in benzene, but of alkyl halides generally in various solvents, present a " unity of mechanism," and necessarily involve " push-pull termolecular " processes; and further that, in benzene, in which the full molecularity can be reflected in kinetic order, " the result is always a push-pull termolecular mechanism with exactly third order kinetics." [1]

Hawthorne and Cram took these ideas as the starting point of an investigation of the reactions of triphenylmethyl chloride with benzyl alcohol, and with several substituted benzyl alcohols, without and with added phenol, in solvent benzene.[2] As this work constitutes the main piece of explicit collateral support for Swain's thesis we have examined its experimental foundations.

Actually, Hawthorne and Cram noticed some kinetic discrepancies. But they left them either poorly explained or unexplained; and they never seem to have been led by them to question the basic validity of Swain's work on which they are attempting to build.

Thus the supposed unity of mechanism was not reflected in their experiments in a

* Part LVI, preceding paper.

[1] Swain *et al.*, *J. Amer. Chem. Soc.*, (*a*) 1948, **70**, 1119; (*b*) p. 2794; (*c*) 1950, **72**, 2794; (*d*) 1951, **73**, 2813; (*e*) 1953, **75**, 136; (*f*) 1955, **77**, 1122; (*g*) p. 3727; (*h*) p. 3731; (*i*) p. 4681.

[2] Hawthorne and Cram, *ibid.*, 1954, **76**, 3451.

unity of kinetic form. Whilst a number of their reactions appeared to fit the third-order rate-law, some, *e.g.*, those with 4-chloro- and 4-nitro-benzyl alcohol in the presence of phenol, required a mixed-order equation,

$$-\mathrm{d[RCl]}/\mathrm{d}t = k_2[\mathrm{RCl}][\mathrm{R'OH}] + k_3[\mathrm{RCl}][\mathrm{R'OH}]^2$$

and a number, *e.g.*, those with benzyl alcohol, and with 4-methyl- and 4-methoxy-benzyl alcohol, in the presence of phenol, fitted the simple second-order equation. As to these last cases, Hawthorne and Cram comment that " the additional third order term was doubtless present, but its effect was always within the experimental error." Now this is an unacceptably poor explanation. For the paper contains an independent way of arriving at these particular k_3 values, and if the experimental error were really large enough to absorb them then it would be at least of the same order of magnitude as *all* the k_3 values quoted (even though they are quoted to three significant figures). This makes nonsense of kinetic support for the termolecular mechanism.

The other main example requires reference to the fact that, just as Swain ran his reactions between triphenylmethyl chloride and hydroxy-compounds in the presence of pyridine (" to take up the hydrogen halide formed " [1a]), so Hawthorne and Cram conducted theirs in the presence of triethylamine. In these conditions, the reaction with phenol was one of those which was said to give agreement with the second-order rate-law. Its absolute rate in the presence of triethylamine was much greater than in the presence of pyridine. These results led the authors to conclude (*a*) that the phenol and triethylamine are practically completely combined to form the triethylammonium phenoxide ion-pair, and (*b*) that the transition state of the measured reaction consists of one molecule of triphenylmethyl chloride and one molecule of triethylammonium phenoxide as ion-pair. They then asked where was the " kinetically invisible " third molecule demanded by the mechanism, not only in this case, but also in the other cases in which the kinetics seemed to conform partly or wholly to a second-order rate-law. They admitted that they could not find a satisfactory answer to that question.

(1) *The Experimental Conditions.*—Hawthorne and Cram examined their reactions of triphenylmethyl chloride with hydroxy-compounds in benzene solutions, which contained triethylamine equivalent to the alkyl halide and were saturated with, and carried in suspension, triethylamine hydrochloride, added initially in solid form in excess, and also precipitated in the course of the reaction. This is a recipe for profound kinetic complications.

In the reaction with phenol they could compare their rate in the presence of triethylamine and its hydrochloride with that obtained by Swain in the presence of pyridine and pyridine hydrochloride. Though there was a large difference, they seem not to have considered the likelihood that almost any moderately basic amine, as a strong nucleophile, must distort the kinetics of reactions of triphenylmethyl chloride with generally less nucleophilic hydroxy-compounds. They do mention that, on working up products, they did not isolate any quaternary ammonium salt. That alone could mean, either that it is formed too slowly, or that it is formed reversibly and rapidly. One may suppose that, ignoring general questions of nucleophilic power, they were excluding the latter interpretation, on account of Swain's statement [1a] that " the reaction between trityl chloride and tertiary amines is negligibly slow." *

We have shown that, as one ought to expect, this statement is not correct (Part LIV), and that, in particular, triphenylmethyl chloride reacts with pyridine and with tri-*n*-butylamine at rates comparable to that of its exchange of chlorine with a saline chloride, and therefore considerably faster than the rates of its reaction with, for example, benzyl alcohol. That no quaternary salt was isolated is irrelevant, because the salt itself

* In the case of triphenylmethyl bromide, Swain and Eddy offer a numerical measure of the slowness, stating that it reacts with pyridine 10^6 times more slowly than with methyl alcohol.[1b]. But they present no account of the experiments on which they base this statement.

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could react with benzyl alcohol, though not at the same rate as the chloride, to which it would concurrently revert.

In Hawthorne and Cram's conditions there are a number of partly compensating disturbances. The net effect of the amine is to reduce the rate of reaction with the alcohol. In principle, the dissolved amine hydrochloride will reduce it further, but this effect is unimportant. However, the suspended salt, 1 g. per 100 c.c. in their conditions, superposes an appreciable surface reaction on the homogeneous one, thus producing a rate increase in the measured overall reaction. The existence of the heterogeneous component implies that any integral reaction order apparently followed by the overall reaction is accidental. All this applies to the otherwise uncatalysed reaction with the alcohol. If we are studying the nucleophilic catalysis of the reaction, as by tetra-*n*-butylammonium perchlorate, then the addition of other nucleophiles, such as tertiary amines and saline chlorides, produces more drastic retarding effects. It is not necessary to record all the details of our survey of this complex situation, because its conclusion is simply that the method must be abandoned. However, the selection of figures in Table 1 will give an idea of the magnitude of the kinetic effects involved.

TABLE 1. *Initial specific rates (k_1 in sec.$^{-1}$) of disappearance of triphenylmethyl chloride by reaction with benzyl alcohol in benzene at 30° in the presence of various added substances.*

(Initially, $[CPh_3Cl] = [C_7H_7{\cdot}OH] = 0{\cdot}05$M, throughout.)

Run no.	$[Bu^n_4NClO_4]$	$[Et_3N]$	$[Bu^n_3N]$	Suspended Et_3N,HCl	10^5k_1
Cf. Table 2	—	—	—	—	0·93
44, 67	—	0·05	—	—	0·50
71, 72	—	0·05	—	1 g./100 c.c.	0·55
110, 128, 182	0·002	—	—	—	23·8
196	,,	—	0·000005	—	16·7
195	,,	—	0·00005	—	2·8
193	,,	—	0·0005	—	2·1

The figures there represent initial specific rates of destruction of triphenylmethyl chloride, $-d[RCl]/[RCl]dt$, as followed by the rate of appearance of acid, or the rate of neutralisation by the acid of initially added base, and derived from the smoothed curve of the early kinetic readings. The basic rate, *i.e.*, with nothing added except the reagents, is really a little too high as given, because of catalysis by adventitious hydrogen chloride, which was present in the experiment cited to the concentration 3×10^{-5}M (cf. the preceding paper, Section 4). However, this does not change the picture, or alter the conclusion that the experimental conditions require to be simplified.

The simplification we have adopted is, of course, to omit the tertiary amine and the amine hydrochloride, and to study initial rates, as illustrated in Table 1. The reaction is reversible, with an equilibrium constant,

$$K = [CPh_3{\cdot}O{\cdot}CH_2Ph][HCl]/[CPh_3Cl][CH_2Ph{\cdot}OH] = 0{\cdot}0065$$

at 30°. But the initial rate of the forward reaction remains steady for long enough to allow it to be determined, before the rate begins to fall on account of reversibility. Dominating autocatalysis, due to developed hydrogen chloride, was not clearly observed, though there can be no doubt that autocatalysis was present and tended to delay the onset of the ultimately dominating retardation due to reversibility. When the reagents were present in equivalence, the forward reaction proceeded to 7·3% of the stoicheiometric maximum; and, naturally, with either reagent in excess, the other was consumed more extensively. For the uncatalysed, or mildly catalysed, reaction, it was easily possible to obtain kinetic points at tenth-per-cent. intervals or less over the first 1—2% of the stoicheiometric reaction, or, say, the first 5—20% of the realisable reaction, and this was adequate for good initial rates. For the faster catalysed reactions, our initial rates are less reliable. The main source of error involved in our method is that of catalysis by adventitious

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hydrogen chloride; but it was not a large error, and ways of coping with it were worked out in some detail as described in the preceding paper.

(2) *Dependence of Rate on the Concentrations of Reactants.*—Our experiments have shown that the benzyl-alcoholysis of triphenylmethyl chloride in benzene is of first order in triphenylmethyl chloride, but has no simple and exact order with respect to benzyl alcohol.

These points, particularly the second, are illustrated in the comparable rate figures given in Table 2. If we plot the logarithm of the specific rate with respect to triphenylmethyl chloride against the logarithm of the concentration of benzyl alcohol, over the investigated 25-fold range of benzyl alcohol concentration, we obtain a continuously steepening curve, with a slope rising from about 1 to 2·5 as the concentration increases, and with no sign of an arrest of slope at 2 or at any other intermediate value.

TABLE 2. *Effect of concentrations of reactants on the initial specific rate (k_1 in sec.$^{-1}$) of disappearance of triphenylmethyl chloride by reaction with benzyl alcohol in benzene at 30°.*

Run	[CPh_3Cl]	[$C_7H_7\cdot OH$]	10^5k_1	% HCl at equilib.*	Equil. const. K
203	0·05	0·020	0·37	4·8	0·0067
211	,,	0·0325	0·63	6·0	0·0065
212	,,	0·040	0·83	6·7	0·0066
69, 102, 116, 133, 163	,,	0·050	0·93	7·3	0·0062
94	0·15	,,	0·93	12·6	0·0063
213	0·05	0·060	1·67	7·6	0·0056
201, 202, 206, 207	,,	0·100	2·77	11·0	0·0072
62, 63, 64, 142, 143	,,	0·150	5·7	12·9	0·0067
74	,,	0·500	67	25·5	(0·0090)
					0·0065

* Calculated taking 0·05M = 100%.

This result for benzyl-alcoholysis is the same as that obtained for methyl-alcoholysis, except that the formal order for methyl-alcoholysis rose just a little more steeply, from about 1 to 3 (instead of to 2·5) in the concentration range over which benzyl-alcoholysis has been investigated; and for methyl alcoholysis the relation was followed to orders below 1 by a downward extension of the concentration range (cf. Fig. 1 of preceding paper). The conclusion is clearly the same: neither two, nor any other small and necessary number of molecules of the alcohol, have exclusive functions and defined positions in the transition state of the rate-controlling step of the measured reaction: there is no "push-pull" by alcohol molecules. This being so, the rest of the argument of Hawthorne and Cram's paper, as of all Swain's papers on this subject, falls to the ground.

This applies, *inter alia*, to a paper by Swain, Moseley, and Bown, to which we have not previously referred.[1h] In it, the push-pull theory was developed on supposedly quantitative lines, which Hawthorne and Cram attempt to apply. In this theory the nucleophile N and electrophile E in the transition state

$$\underset{(n)}{N}\cdots\cdots\underset{(s)}{R}\text{—}\underset{(s')}{Cl}\cdots\cdots\underset{(e)}{E}$$

are assigned factors n and e of pushing and pulling strength, respectively, and the alkyl halide factors s and s' of sensitivity to the pushing and pulling. The law of combination of the factors is assumed to be

$$\log (k/k^\circ) = ns + es'$$

where k° refers to rate with a standard N and E. Obviously, if either or both of the molecules assigned as N and E have not these exclusive functions, *i.e.*, if there is in fact no "push-pull," the considerable numerical elaboration offered in the paper of Swain, Moseley, and Bown cannot have its supposed significance.

The formal order of benzyl-alcoholysis with respect to benzyl alcohol, and the absolute

rate of the reaction, are both still falling as the concentration of benzyl alcohol is reduced, down to the lowest concentration investigated (0·02M). We cannot be sure that the formal order in alcohol would fall to zero at still lower alcohol concentrations, as appears to happen in methyl-alcoholysis; but it is certainly tending in that direction. Furthermore, as the concentration of alcohol is diminished, and the medium is becoming more like pure benzene, the rate is not only becoming less dependent on the alcohol, but is also falling, and is evidently tending to a value well below the lowest recorded in Table 2, *viz.*, $0{\cdot}37 \times 10^{-5}$ sec.$^{-1}$. It is of interest to observe that this lowest recorded rate is already lower than the rate of chloride exchange in benzene, *viz.*, $0{\cdot}503 \times 10^{-5}$ sec.$^{-1}$ at 30°. This makes it clear that these two substitutions of triphenylmethyl chloride, despite that each alone has the kinetic features of an S_N1-type mechanism, are not fully rate-determined by a completely identical process.

Table 2 contains some measurements of the equilibrium composition, as approached from the side of triphenylmethyl chloride and benzyl alcohol. We have done some experiments on equilibrium composition, as approached from the side of benzyl triphenylmethyl ether and hydrogen chloride, and get nearly the same figures, actually very slightly lower ones, when expressed as percentages of hydrogen chloride, probably because of the difficulty of working with all but highly dilute solutions of hydrogen chloride in benzene, from which solvent it escapes somewhat easily.

(3) *Kinetic Effect of Hydrogen Chloride.*—The effects of added substances on the rate of the benzyl-alcoholysis have been investigated less fully than were the corresponding effects on methyl-alcoholysis (see preceding paper), but sufficiently to show that the pattern of kinetic phenomena is generally similar.

The catalytic effect of hydrogen chloride is illustrated in Table 3, which shows that hydrogen chloride increases the rate of the benzyl-alcoholysis, but restricts the extent to which this reaction can proceed. The figures indicate that the measurable kinetic effect is linear, just as for methyl-alcoholysis.

TABLE 3. *Effect of hydrogen chloride on the initial specific rate (k_1 in sec.$^{-1}$) of benzyl-alcoholysis of triphenyl chloride in benzene at* 30°.

(Initially, $[CPh_3Cl] = [C_7H_7{\cdot}OH] = 0{\cdot}05$M, throughout.)

Run No.	10^3[HCl]	10^5k_1	HCl (%) at equil.	Ether (%) at equil.*
403	0·03	0·88	7·3	7·3
405	0·90	2·3	7·6	5·8
404	3·50	6·7	10·0	2·9

* Calc. on the basis 0·05M = 100%.

(4) *Kinetic Effect of Tetra*-n-*butylammonium Chloride.*—Just as for methyl-alcoholysis, so for benzyl-alcoholysis, two phases can be distinguished in the kinetic effect of the progressively added salt. First, very small amounts of the salt will effect a limited depression of the rate, *e.g.*, by 15%. Then, nothing more happens to the rate while the

TABLE 4. *Effect of tetra*-n-*butylammonium chloride on the initial specific rate (k_1 in sec.$^{-1}$) of benzyl-alcoholysis of triphenylmethyl chloride in benzene at* 30°.

(Initially, $CPh_3Cl = 0{\cdot}05$M, and $C_7H_7{\cdot}OH = 0{\cdot}15$M, throughout.)

Run	[Bu^n_4NCl]	10^5k_1	Run	[Bu^n_4NCl]	10^5k_1
Table 2	—	5·7	141, 149	0·02	4·7
153	0·0002	4·8	160	0·04	3·3
146, 159	0·001	4·8	144, 148	0·06	1·9

concentration of salt is further increased by 10 times or even 100 times. But when the concentration of salt begins to approach comparability with the concentration of benzyl alcohol, then a new, and strong, rate-depression sets in. These relations are illustrated in Table 4.

Our interpretation is that the first rate-depression, represented in Table 4 by the reduction of 10^5k_1 from 5·7 to 4·8, arises from the destruction by the added chloride ion of catalysis by the adventitious hydrogen chloride. The chemistry of this is as described in the preceding paper (Section 4). The second rate-depression, that which in Table 4 carries 10^5k_1 from 4·8 down to 1·9 is explained as a common-ion effect in a mechanism of S_N1 type, *i.e.*, an effect of a competition between the saline chloride and benzyl alcohol, for the intermediate formed in an earlier slow step from the triphenylmethyl chloride (cf. preceding paper, Section 5).

In the presence of tetra-*n*-butylammonium chloride, the benzyl-alcoholysis proceeds to an equilibrium, which is strongly displaced in the direction favouring benzyl triphenylmethyl ether and hydrogen chloride. For example, with 0·04M of the salt, ether formation proceeded to more than 50% of the stoicheiometric maximum. This happens because the salt combines with hydrogen chloride to give the corresponding hydrogen-dichloride.

(5) *Kinetic Effect of Tetra*-n-*butylammonium Perchlorate and Nitrate.*—The former salt accelerates the benzyl-alcoholysis strongly; and the latter accelerates it more mildly. This is illustrated in Table 5. We believe that the former effect is the simpler, and that the latter is the net result of partly compensating effects, including the conversion of triphenylmethyl chloride into the corresponding nitrate, with subsequent benzyl-alcoholysis under the retarding influence of the saline nitrate, which is now a common-ion salt.

TABLE 5. *Effect of tetra*-n-*butylammonium perchlorate and nitrate on the initial specific rate (k_1 in sec.$^{-1}$) of benzyl-alcoholysis of triphenylmethyl chloride in benzene at* 30°.

(Initially, $[CPh_3Cl] = 0{\cdot}05$M, throughout.)

Salt = $Bu^n_4NClO_4$, $[C_7H_7{\cdot}OH] = 0{\cdot}05$M throughout			Salt = $Bu^n_4NNO_3$				
Run	10^3 [Salt]	10^5k_1	Run	$[C_7H_7{\cdot}OH]$	10^3 Salt	10^5k_1	HCl (%) at equil.*
Table 2	—	0·93	Table 2	0·05	—	0·93	7·2
119, 127, 130	0·002	1·37	171	,,	2	4·2	>10
114, 118, 129	0·02	4·4	172	,,	10	13·3	25
112, 120	0·2	12·0	173	,,	20	16·6	37
111	1	16·7	Table 2	0·15	,,	5·7	12·9
110, 128, 182	2	23	179	,,	1	8·3	15
109	4	26	180	,,	10	28	31

* Calc. on the basis 0·05M = 100%.

If we plot the logarithm of the increase, produced by the tetra-*n*-butylammonium perchlorate, in the rate of alcoholysis by 0·05M-benzyl alcohol, against the logarithm of the concentration of the perchlorate, we obtain a curve very similar to that already drawn for the increase produced by the same salt in the rate of alcoholysis by 0·05M-methyl alcohol (cf. Fig. 6 of the preceding paper, p. 1250). The central part of the curve conforms to a slope of $\frac{1}{2}$, but the low-concentration extremity runs lower, whilst at concentrations above 10^{-3}M the slope of the curve falls below $\frac{1}{2}$. We take this to mean that the chemistry of the catalysis of methyl-alcoholysis and benzyl-alcoholysis is similar, and that a fuller investigation of the kinetics of the latter would show the same limiting square-root law, representing the inclusion of just one simple perchlorate ion in the transition state of the rate-controlling process. Kinetic deviations arise, without necessarily upsetting this simple meaning, when the salt is so concentrated that it becomes more aggregated than to ion-pairs, and when the medium and salt conditions render perchloric acid somewhat, but only somewhat, less ionised than the corresponding ammonium salt (cf. preceding paper, Section 6).

The addition of tetra-*n*-butylammonium perchlorate has practically no effect on the composition of the equilibrium to which the benzyl-alcoholysis proceeds. On the other hand, the presence of tetra-*n*-butylammonium nitrate, similarly to that of the chloride, shifts the composition at equilibrium in the direction favouring the ether and hydrogen chloride, as is illustrated in Table 5. All this is consistent with the conclusion, reached

in Part LIII that the anion $(ClHClO_4)^-$ does not exist, but that the anions $(ClHCl)^-$ and $(ClHNO_3)^-$ are both stable in benzene.

(6) *Kinetic Effect of Nitromethane and Nitrobenzene.*—These substances were taken as examples of dipolar but aprotic, non-ionic, molecules. As is to be expected, their addition to the non-polar solvent accelerates the polar reaction we are discussing. These kinetic effects are illustrated in Table 6, which also shows that the nitro-compounds have very little effect on the equilibria to which the reactions proceed.

TABLE 6. *Effects of nitromethane and nitrobenzene on the initial specific rate (k_1 in sec.$^{-1}$) of benzyl-alcoholysis of the triphenylmethyl chloride in benzene at 30°.*

Run	$[CPh_3Cl]$	$[C_7H_7{\cdot}OH]$	$[MeNO_2]$	10^5k_1	HCl (%) at equil.*
Table 2	0·05	0·05	—	0·93	7·3
,,	0·05	0·15	—	5·7	12·9
,,	0·15	0·05	—	0·93	12·6
75—78	0·05	,,	0·37	1·85	7·8
86	,,	,,	0·92	2·7	7·2
89, 104	,,	,,	1·85	6·2	7·2
79	,,	0·15	0·37	11·9	13·1
87	,,	,,	0·92	17	13·2
90, 105	—	—	1·85	30	12·8
			$[PhNO_2]$		
80, 82, 83	0·05	0·05	0·97	2·8	7·3
81, 91, 93	,,	,,	1·95	6·0	7·6
84, 85	,,	0·15	0·97	16·7	13·0
88, 92	,,	,,	1·95	24·0	13·0
95	0·15	0·05	1·95	1·8	13·3

* Calc. on the basis 0·05M = 100%.

The increase of rate due to the added nitro-compounds conform to no constant kinetic order with respect to nitro-compound. The formal order increases with concentration, from well below unity to well above it, in the range investigated. This is a common effect on a polar reaction, of the addition of a polar co-solvent to a non-polar solvent. It indicates stabilisation of the transition state by the polar material, partly locally concentrated, but acting mainly by virtue of the great range of electrostatic forces in the non-polar medium: no precise placing of a fixed small number of polar molecules is involved.

(7) *Kinetic Effect of Phenol.*—Added phenol catalyses the benzyl-alcoholysis. It simultaneously acts as a substituting agent, but only to a very minor extent. Its catalytic effect on the alcoholysis was investigated by Hawthorne and Cram,[2] who, however, used only one concentration of phenol, having apparently accepted, as so certain that it was not worth checking, Swain's generalisation that the alcoholysis would be of third order overall, and of first order in phenol, when phenol was present.

Our results for the dependence of the rate on the concentration of added phenol are shown in Table 7, and in the Figure. From the latter one sees that the kinetic order with

TABLE 7. *Effect of phenol on the initial specific rate (k_1 in sec.$^{-1}$) of benzyl-alcoholysis of triphenylmethyl chloride in benzene at 30°.*

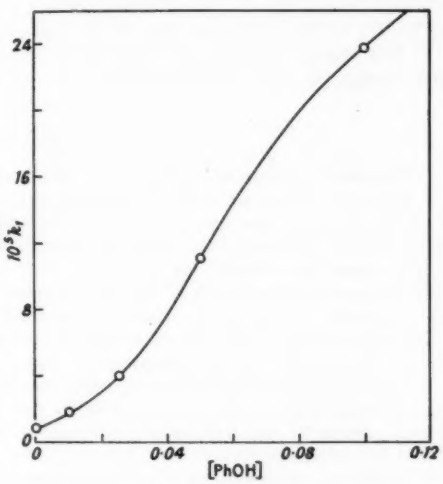
(Initially, $[CPh_3Cl] = [CH_2Ph{\cdot}OH] = 0{\cdot}05$M, throughout.)

Run	PhOH	10^5k_1	Run	[PhOH]	10^5k_1
Table 2	—	0·93	162, 168	0·050	11·1
165	0·010	1·80	167	0·100	23·8
164	0·025	4·0			

respect to phenol is not unity, and is not even constant. In our concentration range it is between 1 and 2, nearer 2 in the central part of the range, but falling towards 1 at both extremities. This is easily verified by plotting the logarithm of the excess of rate against the logarithm of the phenol concentration, when one obtains a sigmoid curve, with slopes varying between 1 and 2. We therefore suggest that the phenol has the function of a

polar co-solvent. We see in these results no evidence that just one phenol molecule has a precise place and an essential function in the transition state of the rate-controlling step of the alcoholysis.

The equilibrium composition of the reaction mixtures was practically unaffected by the added phenol: all the runs in Table 7 developed 6·6—7·0% of the stoicheiometrically possible amount of hydrogen chloride. The reaction of triphenylmethyl chloride (0·05M) with phenol (0·1M), in the absence of benzyl alcohol, came to equilibrium after about 1% of reaction.



Effect of added phenol on the specific rate of reaction of triphenylmethyl chloride (0·05M) *with benzyl alcohol* (0·05M) *in benzene at* 30°.

(8) *Kinetic Effect of Mixtures of Tetra*-n-*butylammonium Perchlorate, Nitrate, and Chloride.*—The available data are in Table 8. Their most striking feature is the great ease with which a second salt, particularly tetra-*n*-butylammonium chloride, destroys the positive catalytic effect of tetra-*n*-butylammonium perchlorate.

TABLE 8. *Effect of mixtures of tetra*-n-*butylammonium salts on the initial specific rate* (k_1 *in sec.*$^{-1}$) *of benzyl-alcoholysis of triphenylmethyl chloride* (0·05M) *in benzene at* 30°.

Run	$[C_7H_7{\cdot}OH]$	$[Bu^n_4NClO_4]$	$[Bu^n_4NNO_3]$	$[Bu^n_4NCl]$	10^5k_1
Table 2	0·05	—	—	—	0·93
171	,,	—	0·002	—	4·2
110, 128, 182	,,	0·002	—	—	23
183	,,	,,	0·002	—	4·7
197	,,	,,	—	0·00005	5·0
Table 2	0·15	—	—	—	5·7
145, 157	,,	0·001	—	—	93
156	,,	,,	—	0·00002	37
158	,,	,,	—	0·00005	18
155	,,	,,	—	0·0001	11·5
152	,,	,,	—	0·001	4·8
147	,,	,,	—	0·02	4·8

The corresponding phenomenon, as observed for methyl-alcoholysis, is shown in the preceding paper to have the correct functional form for interpretation as an effect of the competitive intervention by the tetra-*n*-butylammonium chloride as ion-pair in the second and product-forming step of a reaction rate-controlled by a preliminary step in which the substituting agent does not participate. The criterion is that the reciprocal of the excess rate due to the catalysis, or to the partly suppressed catalysis, would be a linear function of the concentration of the suppressing agent. If we apply this test to the set of runs with

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0·001M-tetra-*n*-butylammonium perchlorate, and various smaller concentrations of tetra-*n*-butylammonium chloride, remembering that the excess of rate must be reckoned, not from $5·7 \times 10^{-5}$ sec.$^{-1}$, a value which includes some catalysis by adventitious hydrogen chloride, but from $4·8 \times 10^{-5}$ sec.$^{-1}$, the asymptotic rate resulting from suppression of the catalysis (Table 4), the reciprocal of the excess of rate is found to conform to a linear function of the concentration of tetra-*n*-butylammonium chloride to within the experimental error. We may accordingly assume that the same interpretation is applicable. The factor, ρ, representing the ratio of the specific rate of capture of a slowly formed intermediate by the suppressing agent, to the absolute rate of its capture by the reagents which lead by the catalytic route to the alcoholysis product, is given by the slope of the linear plot. It is 107,000 mole^{-1} at the concentrations of benzyl alcohol and tetra-*n*-butylammonium perchlorate used in these experiments.

Experimental

Materials.—These were prepared or purified as described in Part LIV.

Methods.—Stock solutions of the component solutes of the reaction mixtures were prepared in benzene, or, in the case of the more difficultly soluble salts, in solutions of benzyl alcohol in benzene. The reaction mixtures were made up in the thermostat at 30·0° + 0·02°, the triphenylmethyl chloride being added last, after the attainment of thermal equilibrium. Samples were quenched in cooled dry benzene and were titrated quickly with 0·05 or 0·01M-solutions of triethylamine in benzene, bromophenol-blue being the indicator. Some samples were quenched in a benzene solution of triethylamine and were then titrated with hydrochloric acid. The results by this method were the same.

Results.—The more important initial specific rates have been cited in previous Tables. Initial rates were taken from smoothed curves of readings taken in the initial parts of runs. These curves do not give steady first-order rate constants, $k_1 = -\mathrm{d}[\mathrm{RCl}]/[\mathrm{RCl}]\mathrm{d}t$, mainly because reversibility leads to a fall after the reaction has proceeded beyond 5, 10, or 20%, according to circumstances, of its way towards equilibrium. The general character of these downward drifts in k_1 is indicated by the examples in Table 9.

Table 9. *Illustrating the calculation of initial specific rates from slowly drifting, integrated, first-order rate constants, obtained from rate curves.*

Run 201. Equilibrium extent of reaction : 11·0%.

Reaction (%)	0·1	0·2	0·3	0·4	0·5	0·75	1·0	1·5
$10^5 k_1$	2·75	2·77	2·63	2·67	2·61	2·50	2·43	2·28

Run 405. Equilibrium extent of reaction : 5·8%.

Reaction (%)	0·2	0·4	0·6	0·8	1·0	1·5	2·0	3·0
$10^5 k_1$	2·25	2·25	2·22	2·20	2·17	2·17	2·13	1·92

Run 155. Equilibrium extent of reaction : *ca.* 13%.

Reaction (%)	1	2	3	4	5	6	7	8
$10^5 k_1$	11·3	11·2	10·7	10·5	10·4	10·4	10·3	10·1

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240. *Mechanism of Substitution at a Saturated Carbon Atom. Part LVIII.* Mechanism of S_N1 Substitutions in a Solvent of Low Solvating Power. A Comparative Discussion.*

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Whilst the results and internal conclusions of the preceding four papers agree in indicating that in each a substitution of S_N1 type is under survey, a comparison of all the results and conclusions reveals a total kinetic pattern sufficiently unprecedented to show that the details of the S_N1 mechanism become significantly modified in solvent benzene.

We have rates of substitution of a common substrate which do not depend on the concentration of the reagent, but do depend on its nature. In concurrent substitutions, we find evidence of competition for a slowly produced intermediate by the reagents, but with competing efficiencies which do not follow the rates of their independent substitutions. We have catalysis of inconstant kinetic order by many polar molecules, including molecular reagents, of all the substitutions, whether by anionic or molecular reagents, and the anionic substitutions are catalysed the more strongly; so that, when an anionic and a molecular substitution are run concurrently, an increase in the concentration of the molecular reagent diverts the primary reaction away from substitution by that reagent. We have strong catalysis by non-reacting salts, particularly perchlorate, of the molecular substitutions; and this catalysis is subject to competitive effects, which show that the active catalyst, kinetically indicated to be the simple perchlorate ion, is attacking a slowly formed intermediate; that is, it is intervening after a slow step, and yet it is providing a by-pass to a rate-controlling step. Finally, such catalysis does not apply at all to the anionic substitutions, which, if affected, are anticatalysed by perchlorate.

This group of results, from any conventional viewpoint largely a collection of paradoxes, is discussed theoretically. It is pointed out that the customary mechanistic deductions from the kinetic form, including mass-law retardation, of S_N1 substitutions is illogically specialised, and that the logically justified, and more general, deductions would include mechanistic modifications capable of accommodating the relations described. These relations are rationalised on the particular basis that S_N1 substitutions in benzene involve two slow, jointly rate-controlling steps, with an intervening fast, product-controlling step. More precisely, a slow ionisation, not entailing dissociation, is succeeded by a fast dipole association, and thereafter by a slow quadrupole rearrangement. The first two steps correspond to the two steps of that more familiar type of S_N1 substitution which prevails in highly solvating solvents; but these steps become modified by the low solvating power of solvent benzene. The modifications render the third step necessary, which therefore owes its existence, and its kinetic significance, to the low solvating power of the solvent. The energetics of the various steps are discussed, and it is shown that the expected energies are physically reasonable, and consistent with experiment.

The immediately preceding four papers, which deal severally with the nucleophilic substitution of triphenylmethyl chloride by chloride ion, azide ion, methyl alcohol, and benzyl alcohol, in solvent benzene, each presents a kinetic picture pointing to an S_N1-type mechanism. Yet, when we compare results among the different papers, we discover kinetic features, which are not encountered in those S_N1 substitutions with which we

* Part LVII, preceding paper.

are most familiar, and which are, indeed, not easy to understand on the basis of the simple formulation usually given to the S_N1 mechanism. We cannot therefore be content just to label our reactions S_N1, and leave the matter there. Some important difference to the detail of this mechanism must have been made when we transferred the reactions to be studied from hydroxylic solvents to solvent benzene. In this paper we try to deduce the nature of the difference. The first step is to get the observations into a single perspective.

(1) *Review of the Observations.*—In this section we shall set down in summary, not all the observations, but all that are relevant to the ensuing argument. The first group relates primarily to the reaction of *chloride exchange*, the substituting agent being tetra-*n*-butylammonium radiochloride (Part LIV).

(C 1) The exchange is of first order in triphenylmethyl chloride, and of zeroth order in the salt. No evidence could be found for a concurrent bimolecular exchange. A bimolecular exchange with the ion-pair as reagent would have produced a kinetic order of unity in salt, and one with the free chloride ion as reagent, an order of one-half in salt; but the order was accurately zero.

(C 2) The specific rates of chloride exchange at 25°, 30°, and 44·6° respectively are 0·320, 0·503, and $1·68 \times 10^{-5}$ sec.$^{-1}$. The Arrhenius activation energy is 16·0 kcal./mole.

(C 3) Added tetra-*n*-butylammonium azide depresses the rate of the chloride exchange, and produces a side-reaction; but it depresses even the initial rate of exchange, thereby indicating a competition between the saline chloride and the saline azide for some slowly supplied intermediate. From the changes in the exchange rate it was deduced that the ratio of the specific rates of capture of the intermediate by the two saline competitors, both acting in ion-pair form, is close to unity.

(C 4) The rate of exchange is much increased by added nitro-compounds, which do not produce side-reactions; but the kinetic order of zero in salt is maintained. The initial rate is also much increased by added amines and by added hydroxy-compounds, which all produce side-reactions; but still the order of zero in salt, with respect to the initial rate, is maintained.

(C 5) The alcoholytic reactions, which accompany chloride exchange in the presence of hydroxy-compounds, are also accelerated by increasing the concentration of the latter, but not so sharply as is the exchange itself. Thus with [MeOH] $< 0·01$M, the methyl-alcoholysis rate, $0·35 \times 10^{-5}$ sec.$^{-1}$, is comparable to the exchange rate $0·32 \times 10^{-5}$ sec.$^{-1}$; but with [MeOH] $= 0·10$M, when both rates are much larger, the alcoholysis rate, $5·6 \times 10^{-5}$ sec.$^{-1}$, is already 8 times smaller than the exchange rate, 45×10^{-5} sec.$^{-1}$, at 25°. Similar effects are observed in exchange in the presence of benzyl alcohol. Thus with [C_7H_7·OH] $= 0·02$M, the rate of benzyl-alcoholysis is 6% of the rate of exchange, but with [C_7H_7·OH] $= 0·05$M, although both rates are considerably increased, the benzyl-alcoholysis rate is only 2·5% of the exchange rate. The same thing holds for the catalysis of exchange by phenol with accompanying phenolysis, though our experiments on this subject were only preliminary, and the figures obtained were not considered good enough to quote. But they do show that in exchange with [PhOH] $= 0·001$M, the rate of the accompanying phenolysis is about 5% of the exchange rate, whereas with [PhOH] $= 0·005$M, when both rates are much increased, the rate of phenolysis has fallen relatively to about 1% of the exchange rate. Always the hydroxylic catalyst, whilst it accelerates both reactions, discriminates against the reaction in which it stoicheiometrically participates.

(C 6) The exchange is not catalysed by tetra-*n*-butylammonium perchlorate, not even in the presence of methyl alcohol, when the salt appears to exert a mildly retarding influence.

The following are the main points which emerged from our study of the *azide-substitution* of triphenylmethyl chloride, with tetra-*n*-butylammonium azide as substituting agent (Part LV).

(A 1) At salt concentrations low enough to secure that nearly all the salt is present

as ion-pairs, or as ion-pairs plus some quadrupoles, this substitution is of first order in triphenylmethyl chloride and of zeroth order in the saline azide.

(A 2) The specific rate of the azide substitution at 30° is $2{\cdot}5 \times 10^{-5}$ sec.$^{-1}$

(A 3) Tetra-*n*-butylammonium chloride, whether added or produced in the reaction, reduces the rate of the azide substitution, thereby indicating a competition between the two saline reagents for some slowly produced intermediate. From the changes in the rate of the azide substitutions, it was deduced that the ratio of the specific rates of capture of the intermediate by the saline competitors, both acting in ion-pair form, is close to unity.

(A 4) The azide substitution is catalysed by phenol, but the catalysed reaction has no particular kinetic order in phenol. This catalysis is comparable in strength to the analogous catalysis of chloride exchange. It is much stronger than the corresponding catalyses of methyl- and benzyl-alcoholyses.

(A 5) The azide substitution is not catalysed by tetra-*n*-butylammonium perchlorate.

We now extract such results as we shall need from our investigation of the *methyl-alcoholysis* of triphenylmethyl chloride in benzene (Part LVI).

(M 1) This reaction is of first order in triphenylmethyl chloride, but except at quite low concentrations of methyl alcohol, it is of inconstant order in methyl alcohol. In the range [MeOH] = 0·002—0·01M, the order in methyl alcohol is approximately zero; but in the range [MeOH] = 0·01—0·5M, the formal order rises continuously from near zero to about three.

(M 2) In the range over which the precise concentration of methyl alcohol is unimportant, [MeOH] = 0·002—0·01M, the specific rate of the methyl-alcoholysis is about $0{\cdot}35 \times 10^{-5}$ sec.$^{-1}$; at [MeOH] = 0·1M it is $5{\cdot}6 \times 10^{-5}$ sec.$^{-1}$, and at [MeOH] = 0·3M it is 137×10^{-5} sec.$^{-1}$, all these values applying to 25°.

(M 3) Added tetra-*n*-butylammonium chloride depresses the rate of methyl-alcoholysis. A minor part of the depression is due to the destruction of catalysis by the hydrogen chloride present in the experiments, but the important depression is of the uncatalysed rate. The functional form of this effect is in approximate agreement with the assumption that the salt in ion-pair form is competing with methyl alcohol for some slowly produced intermediate. From the rate depressions it was deduced that the specific rate of capture of the intermediate by the saline ion-pair is about 5 times as great as the specific rate of its capture by the methyl alcohol molecules, when methyl alcohol is 0·1M.

(M 4) The methyl-alcoholysis is catalysed by nitro-compounds, by phenol, and by hydrogen chloride. Only in the last case is the kinetic order in the catalyst integral and constant. The formal kinetic order in the catalyst rises markedly with the concentration of the nitro-catalysts, rises above unity in phenol, but remains unity in hydrogen chloride. There is also some qualitative evidence of catalysis by free (*i.e.*, solvated) protons.

(M 5) The methyl-alcoholysis is strongly catalysed by tetra-*n*-butylammonium perchlorate. Over the ranges of concentration in which the electrolytic situation can be considered simple, the catalysed reaction has a kinetic order of one-half in the salt. From this, and the quantitative specificity of the catalysis, it was concluded that the catalysing agent is the free perchlorate ion. The catalytic coefficient increases with the methyl alcohol concentration, but the catalysed reaction has not a constant kinetic order in methyl alcohol. The accelerating effect of methyl alcohol on the perchlorate-catalysed alcoholysis is proportionately weaker than its effect on the otherwise uncatalysed reaction.

(M 6) The catalysis by tetra-*n*-butylammonium perchlorate is strongly suppressed by added tetra-*n*-butylammonium chloride, and the functional form of the effect is in agreement with the assumption that the saline chloride as ion-pair is competing for some slowly formed intermediate, with those reagents which carry forward the catalysed reaction. The competing system must involve methyl alcohol, and there is some evidence that it involves the perchlorate ion.

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Finally, we summarise the chief points emerging from our study of the *benzyl-alcoholysis* of triphenylmethyl chloride in benzene (Part LVII).

(B 1) The reaction is of first order in triphenylmethyl chloride, but of inconstant order in benzyl alcohol.

(B 2) As the concentration of benzyl alcohol is progressively reduced, both the absolute rate, and the degree of its dependence on the concentration of the alcohol, continuously diminish; and both were still diminishing at the lowest rate measured, which was $0{\cdot}37 \times 10^{-5}$ sec.$^{-1}$ at 30°. This must be an upper limit to the rate obtaining when the concentration of alcohol is low enough to be unimportant for the rate.

(B 3) Tetra-*n*-butylammonium chloride retards benzyl-alcoholysis, qualitatively as for methyl-alcoholysis (paragraph M 3).

(B 4) Nitro-compounds, phenol, and hydrogen chloride accelerate benzyl-alcoholysis, qualitatively as for methyl-alcoholysis (paragraph M 4).

(B 5) Tetra-*n*-butylammonium perchlorate strongly accelerates benzyl-alcoholysis, and, as far as was investigated, the kinetic pattern of the effect appeared to follow that described for methyl-alcoholysis (paragraph M 5).

(B 6) The catalysis of benzyl-alcoholysis by tetra-*n*-butylammonium perchlorate is very strongly suppressed by tetra-*n*-butylammonium chloride, and the functional form of this counter-catalysis is generally similar to that elucidated for methyl-alcoholysis (paragraph M 6).

(2) *Interpretation: Part* i. *Conclusions from Kinetics apart from Catalysis.*—The picture we shall build of S_N1-type substitutions in benzene, from the above observations, is inevitably more involved than the conventional picture applying to S_N1 reactions in ionophilic solvents. Partly for simplicity, and partly in order to make clear the reasons for the elaborations we shall introduce, we shall develop our interpretation in stages. For the first stage, we need consider only certain observations on the two substitutions by anions. These are the observations on substitution by chloride ion, noted in paragraphs C 1, C 2, and C 3, and those on substitution by azide ion, summarised in paragraphs A 1, A 2, and A 3, of Section 1.

Observation C 1 shows that the rate of substitution by chloride ion is unaffected by the (low) concentration of the saline chloride. The conventional conclusion would be that the measured rate is that of a reaction of some other material, but not of the saline chloride. The kinetic observation shows that the measured reaction is certainly a reaction of the triphenylmethyl chloride. Since this is the only other reagent, the measured reaction, so the argument goes, must be one of this alone. As an anion has finally to be brought into combination to form the product, a cation must somehow be provided; and hence the measured reaction is the ionisation of triphenylmethyl chloride.

In just the same way, observation A 1 shows that the rate of substitution by azide ion is unaffected by the (low) concentration of the saline azide. Again the usual conclusion would be that the reaction of which the rate is measured is not one of the saline azide, but is one of the triphenylmethyl chloride only, which becomes ionised.

If we pursue this argument, it would seem hard to avoid the conclusion that the measured processes in these two substitutions are identical. But observations C 2 and A 2 show that they cannot be, because their rates are different.

We are therefore led to re-examine the logic of the standard kinetic argument; and when we do so, we see that it has a flaw. The logical conclusion to draw from our observation that a measured rate is independent of the concentration of a substance X is simply that the transition state of reaction is formed as easily in one concentration of X as in another. Any particularisation of this conclusion is not necessitated by the observation. The usual particularisation is that X is not present in the transition state. However, another possible particularisation is that X is present, but is so available that, at all practical concentrations, its accession never delays the formation of the transition state, which accordingly has nothing to gain from an increase in its concentration. To adopt

XUM

the first alternative, without further evidence, as has not infrequently been done, is to jump to conclusions, and in our case to a difficult landing.

So let us consider the second alternative. We have triphenylmethyl chloride reacting, in separate experiments, with two reagents X and Y, at rates which, at practical concentrations, are independent of the concentrations of X and Y. But now X and Y are assumed to be ubiquitously present in the transition states. Then the two transition states are different, and so the rates can be different.

We shall now attempt to complement this abstract explanation by setting down some hypothetical chemical schemes which fulfil the conditions it indicates. We commence with a very simple scheme, which qualitatively does so, though we shall find that it is too simple to cover all the observations of which we have to take account.

Suppose that triphenylmethyl chloride RCl is slowly heterolysed to its ion-pair form R^+Cl^-, and that this then instantly attracts to itself the anion X^- of the saline reagent M^+X^- to form the triple ion $X^-R^+Cl^-$, which rapidly breaks down in the two possible ways, to form the factor RCl, and the product RX. We set down two such schemes, representing separate experiments, one with M^+X^- as the reagent, and the other with a second saline reagent M^+Y^-:

$$RCl \xrightarrow[\text{Slow}]{a} R^+Cl^- \xrightarrow[\text{Fast}]{b} X^-R^+Cl^- \begin{cases} \xrightarrow[\text{Fast}]{c} RCl \\ \xrightarrow{d} RX \end{cases} \quad \ldots\ldots\ldots \quad (1)$$

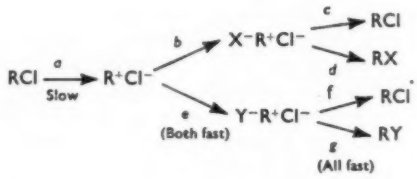
$$RCl \xrightarrow[\text{Slow}]{a} R^+Cl^- \xrightarrow[\text{Fast}]{e} Y^-R^+Cl^- \begin{cases} \xrightarrow[\text{Fast}]{f} RCl \\ \xrightarrow{g} RY \end{cases} \quad \ldots\ldots\ldots \quad (2)$$

The labels "slow" and "fast" describe specific rates, whilst the small letters in the diagram represent instantaneous rates. Then, if no side-reactions occur, for the first experiment, $a = b = c + d$, and, for the second, $a = e = f + g$, at every instant. There will be a ratio $x = d/(c + d)$, which we can call the "yield" of the product RX from the triple ion which produces it. The rate of formation of RX in the first experiment is ax, and is specific to the substituting agent X^-, even though it does not depend on the concentration of M^+X^-, the only concentration on which it does depend being that of RCl. In the second experiment, the yield from the triple ion is $y = g/(f + g)$, and the rate of formation of RY is ay, which is a different rate, and specific to Y^-, though it does not depend on the concentration of M^+Y^-, but only on that of RCl.

We must now refer to the observations C 3 and A 3, which show that, despite the considerable difference in the rates of substitution by chloride ions and by azide ions in separate experiments, when the two substitutions are run together in a common solution, a given fraction of the faster-acting reagent does not proportionately reduce the rate of reaction with the slower-acting reagent by any more than the same fraction of the latter would reduce the rate of substitution by the former. To give a simple example, if the rate of substitution by the pure saline azide, in any concentration within limits, is 50 units, and the rate by the pure saline chloride is 10 units, then any concentration of an equimolar mixture of the two salts will lead to an azide substitution rate of 25, and concurrently a chloride substitution rate of 5 units. Thus the rate of total substitution, as well as the rates of its components, change with the composition of the saline reagent, though not with its concentration at a constant composition. But, even though the absolute rate-changes of the component substitutions are different, the fractional rate-changes, produced by a given fractional dilution of either salt by the other, are the same.

Our scheme allows us to expect a general competitive relation which is independent of the rate difference, and includes the relation described as a special case. This arises as follows. The rate of formation of RX in the separate experiment discussed above depends

on the rate a, and on the rate-ratio d/c: it does not depend in any way on the kinetics of the reaction labelled b. And similarly, the rate of formation of RY in a separate experiment, depends on a, and on the ratio g/f, but not on the kinetics of the reaction labelled e. Now, setting down the scheme for the two reactions running concurrently in the same solution, as in (3) we have $a = b + e$, $b = c + d$, and $e = f + g$; and we see that the



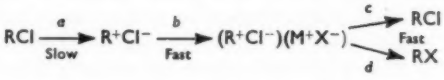
. . . . . (3)

ratio in which R^+Cl^- enters the route that can lead to RX, and the route that can lead to RY, depends, not on the previously important rates, a, c, d, f, and g, but only on the ratio of the other two, previously immaterial rates, b and e. If the corresponding specific rates of these fast processes are B and E, so that $b = B[M^+X^-]$ and $e = E[M^+Y^-]$, then, when we measure the effect of added M^+Y^- on the rate of formation of RX, the intervention constant α_x^y will be E/B; and when we measure the effect of added M^+X^- on the rate of formation of RY, the intervention constant α_y^x will be B/E: each intervention ("mass-law") constant is the simple reciprocal of the other, notwithstanding that the separate substitutions have different rates. The reagents tetra-*n*-butylammonium chloride and azide illustrate an approximation to a special case, inasmuch as both intervention constants were found to be approximately unity. This means that the specific rates of rapid attack by the two saline reagents on the common slowly formed intermediate are about equal ($B \approx E$). A possible reason for this will be suggested later (p. 1274). The point at present is that this approximate equality in competing power does not prevent the reagents from giving their products at quite different rates.

This first step in our interpretation of the kinetic data is so essential that we have chosen to illustrate it with an oversimplified scheme, which in the sequel has to be elaborated in more than one way. One elaboration may be introduced immediately, without looking beyond the limited group of observations on which we are at present concentrating.

The maximum value of a "yield," as we have defined it, is unity. Consider the special case $X^- = {}^*Cl^-$, this $^*Cl^-$ being isotopically labelled, to distinguish it from the chloride ion Cl^- derived from the triphenylmethyl chloride. The triple ion is then symmetrical, except for an isotopic difference, and so $c = d$, and the yield is one-half. Therefore our scheme does not allow a non-isotopic substitution to go at more than twice the rate of the isotopic substitution. But the azide substitution goes at 5 times the rate of the chloride exchange.

Symmetry must therefore be taken out of the relation between the anions and the carbonium ion in the product of the first rapid reaction-step. This product therefore cannot be simpler than a quadrupole, in which each anion occupies a position reflecting its origin:

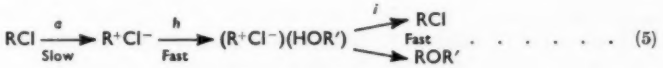


. . . . . (4)

The reason why we write the quadrupole in a linear, rather than a cyclic form, is mentioned below (p. 1276).

Our reaction scheme is still a skeleton, but, as such, it can accommodate the observations from which we developed it. It can similarly accommodate six corresponding

observations on alcoholysis, *viz.*, those summarised in paragraphs M 1, M 2, M 3, B 1, B 2, and B 3, of Section 1. For what the reagent saline dipole is assumed to do, the reagent molecular dipole should be able to do, even if not quite so quickly. The corresponding scheme for alcoholysis with an alcohol R'OH may be written



. . . . . (5)

the " yield " being $z = j/(i + j)$, and the measured rate az.

We know that rate of alcoholysis can approach independence of the alcohol concentration at sufficiently low concentrations, although at higher concentrations a catalytic effect comes in, which can be paralleled by catalysts other than the substituting agent. However, even when the rate does not depend on the reagent concentration, it still depends on the reagent. It is true that the limiting rate of methyl-alcoholysis is nearly the same as that of chloride exchange, but a survey of the rates assembled in Table 1 shows that this particular near-equality is only a coincidence : the rate of benzyl-alcoholysis is smaller, and that of azide substitution larger.

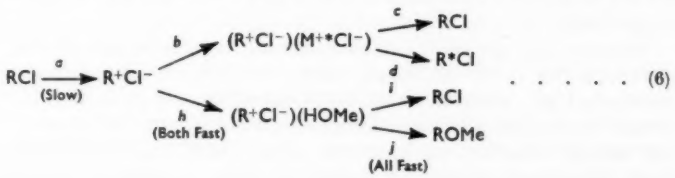
TABLE 1. *Comparison of specific rates of substitution of triphenylmethyl chloride in benzene, when rate depends on the concentration of triphenylmethyl chloride, but not on the concentration of the substituting agent.*

($M^+ = Bu^n_4N^+$; k_1 in sec.$^{-1}$.)

Substituting agent	M^+Cl^-	$M^+N_3^-$	$CH_3{\cdot}OH$	$C_7H_7{\cdot}OH$
10^5k_1 at 25°	0·32	—	0·35	—
,, 30°	0·50	2·5	—	<0·37

In the interpretation represented by our scheme, the yield $j/(i + j)$ in methyl-alcoholysis is nearly the same as the yield $d/(c + d)$ in chlorine exchange, provided that the reagent concentrations are low enough. But when the concentration of methyl alcohol is sufficiently large to make it a significant constituent of the solvent, then, not only are both reactions accelerated, but also they are accelerated unequally, and so, in terms of our interpretation, the yields must become unequal. In 0·1M-methyl alcohol, for example, $d/(c + d)$ is 8 times larger than $j/(i + j)$. A possible reason for this will be suggested later (p. 1272).

When the two substitutions are run together in competition so that $a = b + h$, then the rates, b and h, of the fast steps in which the substituting agents enter reaction, and also their specific rates, B and H, given by $b = B[M^+{}^*Cl^-]$ and $h = H[MeOH]$, are not the same :



. . . . . (6)

For the conditions in which we determined it, the specific rate of capture of the saline ion-pair was about 5 times larger than that of the molecular reagent : $B/H \approx 5$. Whether this ratio is subject to a co-solvent effect of methyl alcohol, is a question that we have still to settle.

(3) *Interpretation : Part* ii. *Conclusions from Kinetics including Catalysis.*—So far we have taken account of only 12 of the 23 observations listed in Section 1. It

is now necessary to consider the remainder, and we shall discuss first a set of 5, *viz.*, those summarised in paragraphs C 4, A 4, M 4, B 4, and C 5.

The first four of these show that all the substitutions are catalysed by various non-ionic but polar molecules. This is true for the anion substitutions, and for the alcoholyses; and in the latter case it remains true when the molecular catalyst happens also to be the substituting agent.

Observation C 5 relates to hydroxy-compounds as catalysts, and particularly to their comparative effects on rate of chloride exchange, and on the ether-forming reactions which accompany exchange in their presence. These catalysts, methyl alcohol, benzyl alcohol, and phenol, always accelerate the chloride exchange more than they accelerate the alcoholytic or phenolytic reaction in which they stoicheiometrically participate.

By comparing rates among the experiments to which paragraphs C 4, A 4, M 4, and B 4 refer, we find that catalysis by polar molecules is generally more marked in the anion substitutions than it is in the alcoholyses. Catalysis by phenol provides a convenient illustration, since this was investigated for all the four reactions studied. 0·05M-Phenol increased the rate of chloride exchange 115 times, that of the azide substitutions 175 times, of methyl-alcoholysis 18 times, and of benzyl-alcoholysis 13 times: the factors of acceleration fall into two orders of magnitude.

Our reaction scheme in its present state of development explicitly shows the ionisation of triphenylmethyl chloride as the one rate-controlling step of all these reactions. Certainly its transition state must be much more polar than its initial state. Indeed, it follows from the general weakness of ion-solvation by benzene, that the transition state of an ionisation in this solvent must resemble the fully formed ion-pair, much more closely than it resembles the initial molecule. Therefore all polar molecules must strongly catalyse the ionisation, by virtue of the much greater interaction of their coulombic fields with the highly polar transition state than with the weakly polar initial molecule.

However, it may be questioned whether this is a complete description of the catalyses that we observe. For consider the catalysis by methyl alcohol of concurrent chloride exchange and methyl-alcoholysis, and particularly the catalytic discrimination against alcoholysis. Despite the great range of coulombic fields in benzene (Part LIII, Section 3), electrostatic catalysis does imply a certain concentration of the catalysing molecules towards the transition state. We should expect that such temporary concentrations of methyl alcohol molecules would increase their local availability, and so would heighten the chance of capture of a newly formed ion-pair of triphenylmethyl chloride by a methyl alcohol molecule, relatively to the chance of its capture by a saline radiochloride ion-pair. The conclusion, deriving from the experimental data, that catalytic acceleration by methyl alcohol diverts the reaction away from the route involving methyl alcohol, makes no sense on this picture. Here we have an indication that the first step of the reaction may not be the exclusive rate-controlling step, and that perhaps rate is determined by some form of joint control.

Thus we may arrive at the idea that all these substitutions may have a second rate-controlling step. We can already assign to it some necessary properties. The immediate precursor of the assumed second rate-controlling step in methyl-alcoholysis must already contain the methyl alcohol molecule which is to react, in order that the reacting system shall not be dependent on acquiring one of those ambient molecules of methyl alcohol, whose local concentration we change when we investigate catalysis by methyl alcohol. Presumably an analogous inclusion of the substituting agent will have occurred in the same stage of the other substitutions. This is consistent with the generally stronger catalysis by polar molecules of anion exchange than of alcoholysis, a difference which must mean that the transition state of the second and final rate-controlling step of the anion substitution has a more inhomogeneous coulombic field, and therefore a field which interacts more strongly with the ambient dipoles than does the field of the transition state of the corresponding step of alcoholysis. This is intelligible if the place of the alcohol

molecule in alcoholysis is being taken by the saline dipole, with its two fully formed ions, in the immediate precursor of the final transition state of the anion substitution.

We reach similar conclusions, if we consider the remaining set of 6 observations, *viz.*, those applying to catalysis by salts, especially tetra-*n*-butylammonium perchlorate, as described in paragraphs M 5, B 5, C 6, A 5, M 6, and B 6, of Section 1.

Observations M 5 and B 5 show that the catalysis of alcoholysis by this salt is very strong, and is of such kinetic form that the active agent may be concluded to be the free perchlorate ion. The catalysis is so strong, expecially considering that the attainable concentrations of this anion are only of the order 10^{-10}—10^{-9}M, that we must regard it as involving a drastic short-circuiting of some rate-controlling step.

However, observations C 6 and A 5 show that the reactions of anion substitution are not similarly catalysed by perchlorate. Therefore it is not possible to identify the step which is being by-passed, with a step which is common to all the substitutions, alike by molecular reagents and by anions. Also, if perchlorate ion could catalyse the initial ionisation, the chloride ion and the azide ion should be able similarly to intervene in this step, and that would produce bimolecular chloride exchange, and bimolecular azide substitution for which reactions we could find no evidence (paragraphs C 1 and A 1 of Section 1).

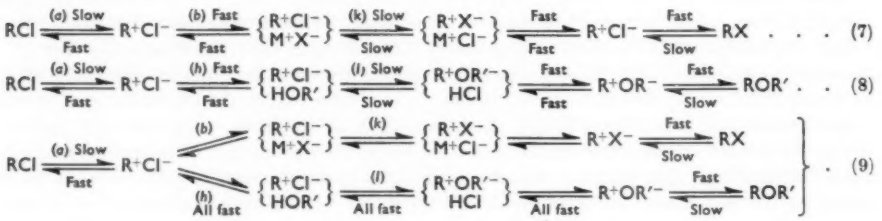
Furthermore, observations M 6 and B 6 show that the catalysis of alcoholysis is very strongly repressed by tetra-*n*-butylammonium chloride, and that the functional form of this counter-catalysis points to a competitive intervention by the suppressing agent in a fast process for some slowly formed intermediate. The active counter-catalytic agent is almost certainly the tetra-*n*-butylammonium chloride ion-pair. There is qualitative evidence that what it competes against is a combination involving both the alcohol and the perchlorate ion, though we have still to prove this quantitatively. The position thus appears to be that the perchlorate ion is intervening after a slow step, and yet it is by-passing a slow step; and that it can itself be by-passed by the product-determining step of an anion substitution, which it does not catalyse. So again we arrive at the picture of two rate-controlling steps, with a fast product-determining step, in which the substituting agent is fully captured, interposed between them.

Now this idea is really contained in the reaction schemes already written, even though they do not show it, provided that we accept the principle of microscopic reversibility at least in its application to sufficiently slow processes. Consider, for example, scheme (4) (p. 1270), with X specialised to *Cl, the asterisk signifying an isotopic distinction. The quadrupole appearing in the scheme, in our special case (R^+Cl^-) ($M^{+*}Cl^-$), has a fast route, labelled *c*, by which it can revert to RCl. But there can be no faster route of reversion than the retracing of the steps, labelled *a* and *b*, by which the quadrupole was formed from RCl. Now it will be recalled that we had to keep anion-symmetry out of the quadrupole, in order that the yield, $d/(c + d)$, in chloride exchange could be less than one-half; for our rate comparisons indicated that it was indeed less. In other words, we had so to shape the scheme that process *d* would be somewhat slow compared with process *c*. In our special case, the product of process *d* is R*Cl. Now consider process *d* in reverse. The fastest route back from R*Cl to the quadrupole (R^+Cl^-) ($M^{+*}Cl^-$) must consist simply in a retracing of route *d*. But since R*Cl has exactly the same chemical properties as RCl, this retracing must start with two steps like *a* and *b*, and so must lead first to a stereoisomeric quadrupole ($R^{+*}Cl^-$) (M^+Cl^-). To complete the backward process, we have to interconvert the two quadrupoles, and that is a step which must obviously pass through a transition state with anion-symmetry, and have the same rate in both directions. This step, therefore, has to be introduced also into the forward process *d*; and it is the only step which could make process *d* slower than process *c*. It is implied that the isomerisation of quadrupoles is an activated process. Its energy of activation can only be electrostatic, but we shall see presently that the required energy could be quite sufficient.

This argument, based on the principle of microscopic reversibility, is most simply set

down for the case of isotopic substitution. We could develop arguments, which are inevitably longer, but have the same end result, for all the substitutions: in all of them, the second slow step is a quadrupole rearrangement. In anion substitutions, its activation energy is wholly electrostatic. In the substitutions by non-ionic reagents, the activation energy is partly covalent and partly electrostatic. The transition states will involve a similar disposition of the two anions or potential anions, with respect to the carbonium ion. Thus in anion substitution, the transition state of the quadrupole rearrangement can, as one possibility, be regarded as a carbonium ion centred against a saline triple anion. In the alcoholytic substitutions, it can be considered as a carbonium ion similarly associated with a hydrogen-bonded, and hence semi-electrovalent, complex anion $(Cl\cdots H\cdots OR')^-$.

In accordance with these considerations, we may now rewrite scheme 4, and similarly schemes 5 and 6 (the last with some generalisation), in the fully explicit forms 7, 8, and 9, respectively.* For the steps of the forward reactions, we retain the previous letter-labels as far as applicable, and introduce some new ones for the quadrupole rearrangements:



(7)

(8)

(9)

It will be obvious that the results considered in Section 2 can be accommodated by these expanded schemes. In particular, substitution rate can depend on the nature, but not on the concentration, of the substituting agent; the rate of a substitution can not only be smaller than the isotopic exchange rate, but can also be greater, in particular greater than twice that rate; yet the substitutions show, in a completely normal way, the competitive effects characteristic of S_N1 reactions.

Even the apparently coincidental result, that tetra-*n*-butylammonium chloride and azide, though they substitute at quite different rates, have almost identical competing effciencies, seems rational. For competing efficiency depends on the first fast step (*b*) of each of these substitutions. The driving force in this step is electrostatic, a dipole–dipole attraction of fairly long range, which should be nearly identical as between the alkyl halide ion-pair and two saline ion-pairs of similar dipole moment.† The important resisting forces in this fast process are probably those of viscous transport, and their main determinant will be the electrokinetic mobility of the large tetra-*n*-butylammonium ion, which is the same for both salts. Thus the competing efficiencies of the two salts should be very similar.‡ The difference in their rates of reaction depends, not on the fast step (*b*), but on the slow succeeding step (*k*); and this is a matter of detailed local geometry, and of short-range forces, which will be considerably different for the two substitutions.

There is no difficulty in understanding on these lines the result that the competing efficiency of the alcohols is smaller than that of the salts, even though the rate of reaction

* Perhaps in schemes 8 and 9, $R^+OR'^-$ and ROR′ should be rewritten with inclusion of a proton in each case.

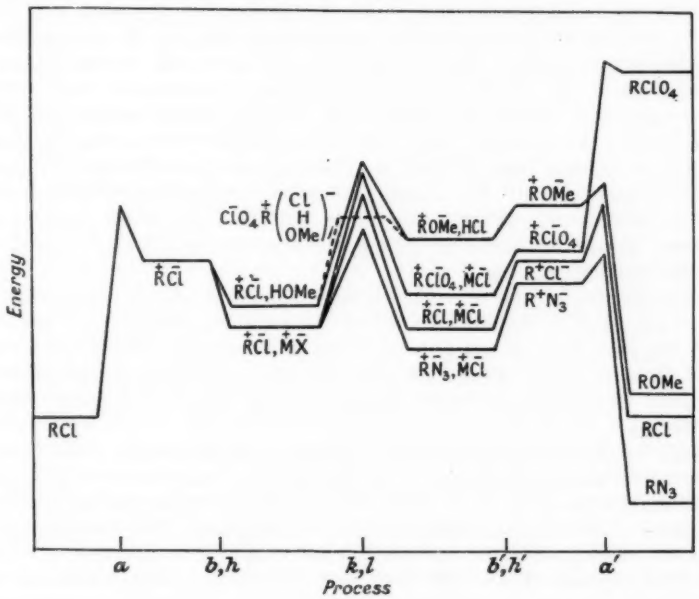
† We infer the similarity of the saline dipole moments from the practically identical ion-pair parameters a_2 of our salts, and from Fuoss and Kraus's direct measurements of the dipole moments of some similar salts in benzene (cf. Part LIII, Table 1, and ref. 7). We have not yet directly measured the dipole moments of our salts, but intend to do so.

‡ Dipole association will normally be complete in less than 10^{-6} sec.

of an alcohol is not necessarily smaller than that of a salt, as has been illustrated for methyl-alcoholysis in comparison with chloride exchange.

It will facilitate the further discussion of catalysis to think of schemes (7), (8), and (9) qualitatively in terms of the energy changes they imply. The overall energy of activation is the endothermicity of the ionisation, (*a*), minus the exothermicity of the dipole association, (*b*) or (*h*), plus the energy of activation of the quadrupole rearrangement, (*k*) or (*l*). For ease of back-translation to reaction rates, we can consider entropy terms as always included, so that all our energies are really free-energies. For each substitution, we can take the energy of the initial state as the arbitrary zero, so that for all substitutions

Schematic energy-configuration curves, representing the theory of joint rate-control by ionisation and quadrupole rearrangement, with intervening product-control by dipole association, in S_N1 *substitutions in a weakly solvating solvent* ($X^- = Cl^-$, N_3^-, or ClO_4^-).



it is the same, and we have not to think about the energy of the substituting agent until it becomes associated with the substrate. The energy scale is also arbitrary to the extent that, if we draw an energy curve for a particular substitution under given conditions, and then proceed to use it in a discussion of catalysis, we must regard the levels and summits as shifted downwards in energy, some more than others, by the addition of a catalyst, or by an increase in the concentration of a substituting agent which acts also as a catalyst. These are the conventions on which the schematic diagram of the Figure has been constructed, in which we have introduced the further simplification of assuming that the energies of association of the common substrate ion-pair, R^+Cl^-, with the three saline ion-pairs M^+Cl^-, $M^+N_3^-$, and $M^+ClO_4^-$, collectively symbolised M^+X^-, are the same. We do this because the competition experiments indicated that it is approximately true for M^+Cl^- and $M^+N_3^-$, though we cannot verify it for $M^+ClO_4^-$, because the high energy (*i.e.*, the practical non-existence) of covalent $RClO_4$ prevents this reagent from yielding a product. And so in the diagram the curves for the three salts do not spread out before the stage of quadrupole rearrangement. Again for simplicity, the labels attached to the

energy levels express only what is associated with triphenylmethyl R; but the energies of the reagent or eliminant must be understood to be included.

We may here indicate why we think quadrupole rearrangement can provide a significant contribution to the energetics The basic reason is that a very substantial fraction of the total work of separating any two fairly small ions in a weakly solvating solvent is done in the first Ångstrom of separation, and temporary charge separations of that order are involved in rearrangements.

We cannot, of course, attempt anything more than an order-of-magnitude calculation, but for this purpose the following rough models will serve. For the tetra-*n*-butylammonium ion, we take a sphere of averaged radius 4 Å: such spheres would pack to a reasonable liquid density if the net charge were taken out. For either anion, we assume a sphere of radius 2 Å, which is approximately right for a chloride ion. For the triphenylmethyl carbonium ion, when free, or in symmetrical immediate surroundings, we take a cylinder, of average van der Waals radius 5 Å, and effective thickness 5 Å, dimensions which give a reasonable packing density, the thickness allowing for the necessarily large twisting of the phenyl groups; and we take the charge as central, though it must actually be spread over the volume of the ion. When this cation is associated with a single anion, it probably goes into a mildly pyramidal form, with the charge rather well localised on the central atom. We represent this form of the cation by replacing the faces of the former cylinder by a projecting and a re-entrant blunt cone, each of height 1 Å, representing a bond-bending angle near 10°, *i.e.*, a degree of bending about half-way towards tetrahedral bending; and now we assume the charge to be only 1·5 Å behind the projecting apex, in order that the charge separation in an ion-pair shall be nearly what it would be in a corresponding aliphatic ion-pair.

With these models, we can conveniently work at first in units $10^8e^2/D$, where e is the electronic charge, and D the effective dielectric constant: energy terms are then given directly by the reciprocals of charge separations in Ångstroms. The total energy of the ion-pairs M^+Cl^- and R^+Cl^-, when widely separated, is $-0{\cdot}453 + \varepsilon$ units, where ε is the bending energy of the carbonium ion, and the energy zero is the energy with all ions widely separated.

In general, dipoles may associate either laterally or longitudinally, lower energies being attained by lateral association if the dipoles are long and thin, and by longitudinal association if they are short and thick. In our case, the most stable quadrupoles arise by longitudinal association. There are two possible linear quadrupoles. One of them is of the form $(M^+Cl^-)\,(R^+Cl^-)$, and presumably contains the flat form of R^+; its energy is $-0{\cdot}472$ unit. The other is of the form $(R^+Cl^-)\,(M^+Cl^-)$; and, if we assume that it contains the mildly pyramidal form of R^+, its energy will be $-0{\cdot}495 + \varepsilon$ units. This is probably the more stable form of the quadrupole, since ε is a somewhat small energy quantity.

There are two possible types of symmetrical transition state. In one, which we symbolise $R^+(Cl^-M^+Cl^-)$, the triple anion spreads itself across the flat, or the obtusely conical, face of the carbonium-ion model. If we assume the flat model, the energy of this transition state is $-0{\cdot}366$ unit. If we take the conical model, the energy is $-0{\cdot}391 + \varepsilon$ units. The latter form is probably the more stable. In the other type of transition state, which we may symbolise $M^+(Cl^-R^+Cl^-)$, the ammonium ion M^+ occupies the median plane of the flat carbonium ion, while the chloride ions occupy symmetrical positions near the centre of the carbonium ion. The energy of this state is $-0{\cdot}422$ unit; and so this is the most stable of the transition states considered. It does not become still more stable when the Cl^- ions are moved in parallel away from the R^+ centre towards M^+.

Considering now only the most stable of the quadrupoles and transition states, we find that the exothermicity of quadrupole formation is 0·042 unit, and that the activation energy of quadrupole rearrangement is $0{\cdot}073 - \varepsilon$ units. We cannot compute the bending energy ε, but it is probably small enough to be neglected in so rough a calculation. If we assume this energy to be $\frac{3}{2}\Gamma\theta^2$, where Γ is the bending moment-constant, and θ is

the angle through which each carbonium-ion bond is bent out of its original plane, then with $\Gamma = 10^{-12}$ dyne-cm./radian, the bending energy comes to 0·8 kcal./mole. Our energy values are much more seriously affected by what we take for the effective dielectric constant D. Obviously we have not to take orientation polarisation into account, but only electron polarisation, whether of the reacting species or of benzene; and since the refractive indices of so many compounds of octet structures are near 1·5, it should be fairly satisfactory to take the square of this, 2·25, which also happens to be the dielectric constant of benzene. With this value of D, our energy unit is equal to 148 kcal./mole; and so the exothermicity of quadrupole formation is 6 kcal./mole, and the activation energy of quadrupole rearrangement is $10{\cdot}8 - \varepsilon$, or, say, 10 kcal./mole.

The experimental activation energy for chloride exchange is 16 kcal./mole (Section 1, paragraph C 2). If we should accept the figures derived by calculation, the heat of ionisation of the triphenylmethyl chloride in benzene would become $16 - 10 + 6 = 12$ kcal./mole. We cannot calculate the separate activation energies of ionisation, and of covalent formation from ions, of triphenylmethyl chloride, but the latter must be much smaller than the former, and so smaller than 12 kcal./mole. It may possibly be almost zero. According as it is, or is not, smaller than 4 kcal./mole, the overall activation energy will, or will not, be greater than the activation energy of the primary ionisation. We are not so much concerned here with actual values as with showing by a calculation based on models, that, in a solvent such as benzene, primary ionisation will be succeeded by a number of electrostatic processes of ionic regrouping, each of such energetic importance that their sum can quite well determine a kinetically significant difference between the activation energy of the primary ionisation and the overall activation energy, and therefore between rate of ionisation and overall rate. Needless to say, quadrupole formation and rearrangement might lead to an entropic rate factor of some importance, but our present models are too crude to allow us theoretically to investigate this possibility.

Hudson and Saville's remark [1] that reactions similar to those here studied might pursue mechanisms intermediate between the mechanisms S_N1 and S_N2C^+, suggests another possible approach to modified S_N1 mechanisms, such as that now described.*

We return now to the subject of catalysis. As to catalysis by polar molecules, a catalysis common to all the substitutions, the most important things have been said, but the Figure will perhaps make it clearer that such catalysis is a composite phenomenon. Ambient dipoles will statistically dispose themselves about every polar configuration of reactants in such a way as to reduce its energy. They will thus lower the activation energy of the preliminary ionisation; and partly on this common account, but partly also on account of their effect, by the same electrostatic mechanism, on the exothermicity of dipole association, and on the activation energy of quadrupole rearrangement, they reduce the overall activation energy. Because each of the last two contributions to the total effect will change from one substitution to another, the overall reduction of activation energy will be different for the different substitutions. We have already ascribed the stronger catalysis by polar molecules of anion substitution than of alcoholysis to the more polar character of the rearranging quadrupole in anion substitutions. In the Figure, the curves for chloride exchange and methyl-alcoholysis are drawn as though such catalysis had already reduced the activation energy of the former reaction below that of the latter.

A more specialised problem is presented by the catalytic action of salts, in particular, of tetra-*n*-butylammonium perchlorate. This catalysis is specific for alcoholysis, and does not apply to anion exchanges. The kinetic effect followed the square-root of the salt concentration, and it was accordingly concluded in Part LVI that the active agent is the simple perchlorate ion (there being obvious reasons why it was not the tetra-*n*-butyl-

* As to S_N2C^+ reactions, cf. Gelles, Hughes, and Ingold, *J.*, 1954, 2918. Some interesting new examples, though they are not so labelled, have been given by Bethell and Gold (*Chem. and Ind.*, 1956, 741).

[1] Hudson and Saville, *J.*, 1955, 4138.

ammonium ion). Earlier in this Section, we concluded that this anion intervenes between the two slow steps, and that it replaces the transition state of the second by some markedly different transition state.*

The general reason for the selectivity of this catalysis seems fairly clear. If the perchlorate ion were to attack the first-formed quadrupole in chloride exchange, or in azide substitution, its most probable action would be to displace the saline anion, thereby giving an energetically nearly equivalent quadrupole (R^+Cl^-) ($M^+ClO_4^-$), which cannot give a reaction product. Therefore the perchlorate ion does not catalyse. In a pure benzene solvent, there is never enough of it to render noticeable a retarding action, due to temporary sheltering of R^+Cl^- in the perchlorate quadrupoles. With the larger concentrations that can be introduced into benzene containing methyl alcohol, we may have observed a depression, by added perchlorate, of the initial rate of chloride exchange; but it is difficult to be sure, because, as explained in Part LIV, there is, in these circumstances, a progressive apparent retardation, due to a radioactive dilution of the original radiochloride, in consequence of the concurrent alcoholysis.

When the perchlorate ion attacks the corresponding alcoholytic quadrupole, the only anion it can displace is that derived from the original triphenylmethyl chloride; and this is a much more complex process. A half-way stage in it might be depicted as a triple ion, (*A*) with a hydrogen-bonded anionic component. This will proceed to lose HCl, and then can lead only to the product ROR'. These may be metastable configurations on the way to the configuration represented, which itself might be a transition state, or might have metastability. The critical part of the catalysed process of methyl-alcoholysis is represented in the Figure by a broken line, as a signal that we have now changed our energy zero in a new way, by including everywhere the energy of the perchlorate ion, which is not stoicheiometrically a reactant. But with this convention, the energy of the hydrogen-bonded triple ion must lie lower in the diagram than that of the half-rearranged quadrupole for alcoholysis without perchlorate.

$$ClO_4^-R^+\begin{pmatrix} Cl \\ H \\ OR' \end{pmatrix}^- \qquad (A)$$

We can understand the observation that the superposed catalytic effect of methyl alcohol on the perchlorate-catalysed alcoholysis is weaker that the catalytic effect of methyl alcohol on the otherwise uncatalysed alcoholysis. For the perchlorate-catalysed reaction has, in its initial state, a free perchlorate ion, which must lose some of its external field when it becomes bound in the transition state.

An added saline chloride must be assumed to turn perchlorate out of the complex triple ion, and so determine reversion to the quadrupole (R^+Cl^-)(HOMe), or, if enough chloride is added, to the quadrupole (R^+Cl^-)(M^+Cl^-); so that, according to the quantity employed, we return to the unaccelerated, or to a retarded, alcoholysis. The sensitiveness

* Winstein and his co-workers (Fainberg and Winstein, *J. Amer. Chem. Soc.*, 1956, **78**, 2763, 2769, 2780; Fainberg, Winstein, and Robinson, *ibid.*, p. 2777; Winstein and Clippenger, *ibid.*, p. 2784) have described what they call a "special" accelerative effect of low concentrations of lithium perchlorate on the solvolysis of certain alkyl sulphonates in acetic acid. As far as we can see from the figures given, this acceleration is not so far from proportionality to the square-root of the salt concentrations that one should not consider assigning it to the simple perchlorate ion of the slightly ionised salt. At higher concentrations of salt, a linear acceleration sets in, which it would seem reasonable to ascribe to saline ion-pairs. The authors seem not to have considered that the two accelerations might arise from different saline species. They emphasize strongly, to the point of illustrating (twice) that a displayed linear relation, when replotted semilogarithmically, gives a curve, that they never find a linear dependence of the logarithm of the rate on the salt concentration, a form of relation which we deduced some time ago from ion-atmosphere theory, and illustrated by solvolysis in aqueous acetone (Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 979). Here they forget that ion-atmosphere theory would be inapplicable to the salts employed in solvent acetic acid (as in some other solvents they mention), in which, at the concentrations of the measurements, lithium perchlorate, for example, would exist almost entirely as ion-pairs, in equilibrium with relatively few simple ions. Thus the ion-pair concentration would be nearly equal to the salt concentration, whilst the free-ion concentration would be proportional to the square-root of the salt concentration. In regard to range of penetration by Coulombic forces, acetic acid, of dielectric constant 6·2, is a very weakly polar solvent, probably because most of its molecules are cyclic dimers of zero dipole moment. The kinetics of S_N1 reactions in acetic acid might therefore have some features in common with their kinetics in benzene, including the possibility of involvement of the substituting agent after ionisation, but before rate is fully determined.

of the counter-catalysis, can be ascribed to the low concentration of available perchlorate ion, and to the energy differences between the complex triple ion and the quadrupoles.

This concludes our comparative discussion of the observations in the preceding papers. The group of observations as a whole presents many features which have little precedent, and it would be too much to hope that our attempts to include them in a self-consistent interpretation is correct in all particulars. However, the general idea than an S_N1 reaction in a weakly solvating solvent may involve more than one stage of rate-control, with intervening product-control, seems to cover the facts so far established. It is a concept that we shall certainly try to test further.

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241. *Mechanism of Substitution at a Saturated Carbon Atom. Part LIX.* Kinetics and Mechanism of the Reaction of Methyl Bromide with Pyridine in Benzene.*

By Y. POCKER.

In contrast to the S_N1 substitutions of triphenylmethyl chloride in benzene, as described in the preceding papers, the reaction of methyl bromide with pyridine is of first order in each reagent, and is subject to only very weak catalysis by hydroxy-compounds, and to weakly accelerative effects of salts, including a common-ion salt (bromide). All the forms of catalysis are ascribed to macroscopic medium effects of added polar molecules or saline ion-pairs, and it is concluded, contrary to Swain and Eddy, that an S_N2 mechanism is under observation.

The rates and their thermodynamic factors, reported here and by Winkler and Hinshelwood, for Menschutkin reactions in benzene, are compared with those, given by de la Mare *et al.*, for Finkelstein reactions in acetone. The similar effects of structure show that both substitutions have the same molecularity, *i.e.*, that both are S_N2 reactions.

SWAIN and EDDY [1] investigated the interaction of methyl bromide with pyridine in solvent benzene, and included it as an example of Swain's " push-pull termolecular " mechanism.

The writer concurs with Hughes and Ingold [2] in regarding it as an S_N2 substitution, but one subject to co-solvent accelerative effects when dipolar substances are added to the non-polar solvent, benzene, because charges are being created in the reaction, and therefore its transition state is more polar than its initial state :

$$C_5H_5N + CH_3Br \longrightarrow [C_5H_5\overset{\delta+}{N} \cdots CH_3 \cdots \overset{\delta-}{Br}] \longrightarrow \{C_5H_5\overset{+}{N}CH_3\}\overset{-}{Br}$$

The reaction goes at a convenient speed at 100°, and its product is thermodynamically stable enough to enable the kinetics of the forward process to be investigated without trouble from reversibility. The present re-investigation of the reaction seemed desirable in order to bring out the contrasts, which Swain and Eddy's paper do not make clear, between its kinetics, and the kinetics of those S_N1 substitutions in benzene, which form the subject of the immediately preceding papers.

* Part LVIII, preceding paper.

[1] Swain and Eddy, *J. Amer. Chem. Soc.*, 1948, **70**, 2989.
[2] Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell, London, 1953, p. 357.

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(1) *Kinetics and Mechanism of the Reaction of Methyl Bromide with Pyridine in Benzene.*— The first contrast is that, whilst the reactions of triphenylmethyl chloride are of first order in this substance, and of zeroth order in substituting agents at low concentration, the reaction of methyl bromide with pyridine is of first order in each reagent. This is established by the constancy of the second-order rate coefficients in runs with different initial concentrations of either reactant as shown in Table 1, and also (in agreement with Swain and Eddy) by the kinetic course of the individual runs, as illustrated in Table 6.

TABLE 1. *Second-order rate-constants (k_2 in sec.$^{-1}$ mole^{-1} l.) of the reaction of methyl bromide with pyridine in benzene at* 100°.

Run	[MeBr]	[C_5H_5N]	10^4k_2	Run	[MeBr]	[C_5H_5N]	10^4k_2
48	0·06	0·20	4·70	49	0·12	0·20	4·70
1	0·12	0·10	4·69	3	,,	0·30	4·72
2	,,	0·20	4·70	4	0·24	,,	4·75

The catalytic effects of added alcohols and phenol are much smaller in this reaction than in the investigated substitutions of triphenylmethyl chloride. Thus whilst 0·1M-methyl alcohol produces a 1700% increase in the rate of alcoholysis of triphenylmethyl chloride, and a 14,000% increase in the rate of its halide exchange, it leads only to a 14% increase in the rate of reaction of methyl bromide with pyridine. Further illustrations of the contrast are given in Table 2.

Benzyl alcohol, phenol, and also nitrobenzene accelerate the reaction as much as, or more than, methyl alcohol does; but none of these accelerations is really large, as can be seen from the general comparison in Table 3. Neither the alcohols nor phenol reacts with

TABLE 2. *Effect of added methyl alcohol on the second-order rate-constants (k_2 in sec.$^{-1}$ mole^{-1} l.) of reaction of methyl bromide with pyridine in benzene at* 100°; *and comparison of the percentage accelerations produced by methyl alcohol in this reaction and in substitutions of triphenylmethyl chloride in benzene at* 25° (*cf. Parts LIV and LVI*).

Initially, [MeBr] = 0·12M and [C_5H_5N] = 0·20M, throughout.

MeBr + pyridine			Increase (%) of rate		
Run	MeOH	10^4k_2	MeBr + Py	Ph_3CCl + MeOH	Ph_3CCl + M^+Cl^-
2, 49	0·00	4·70	0	0	0
19	0·01	4·75	1	23	—
17	0·02	4·80	2	110	55·5
20	0·05	5·00	6	530	—
18	0·10	5·35	14	1700	14,000
16	0·20	6·00	28	11,400	—
21	0·50	7·95	69	123,000	—

TABLE 3. *Effect of molecular addenda on the second-order rate-constants (k_2 in sec.$^{-1}$ mole^{-1} l.) of reaction of methyl bromide with pyridine in benzene at* 100°.

(Initial concns. as in Table 2.)

	MeOH	CH_2Ph·OH		PhOH		Ph·NO_2	
[Addendum]	10^4k_2	Run	10^4k_2	Run	10^4k_2	Run	10^4k_2
0·01	4·75	24	4·75	4	4·85	11	4·70
0·02	4·80	22	4·80	8	5·10	—	—
0·05	5·00	25	5·07	5	5·68	14	4·95
0·10	5·35	23	5·60	6	6·60	12	5·27
0·20	6·00	26	6·37	7	8·26	15	6·00
0·50	7·95	27	10·0	10	11·7	13	8·85

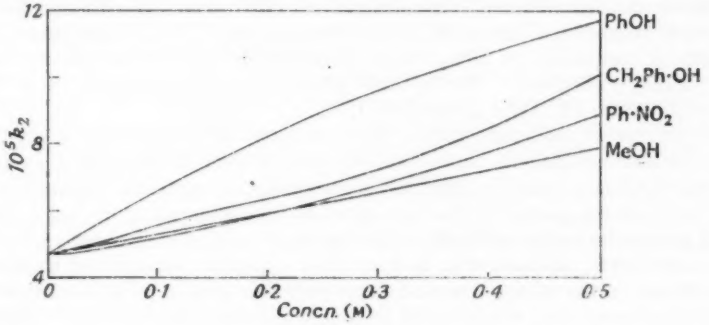
methyl bromide in benzene in the absence of pyridine at rates which are significant in comparison with the rates of the reaction with pyridine.

As all these catalytic effects are somewhat small, it is not to be expected that they would deviate strikingly from linearity; but that they are in general non-linear will be

clear from the rate–concentration curves shown in the Figure. It is difficult, therefore, to agree with Swain and Eddy in their arguments, (*a*) that the accelerative effects of added hydroxy-compounds are too large to admit of interpretation as polar co-solvents effects, and (*b*) that the accelerative effects are to be regarded as linear, in accordance with Swain's termolecular theory. It should be said that these authors offer no acceptable experimental evidence in support of these conclusions, and, in particular, no proof of the assumed constancy of reaction-order in the added substances. In illustrating their discussion, they formulate the termolecular theory with phenol as the third molecule; but they record only one experiment with added phenol.

An examination has been made of the kinetic effect of three salts, *viz.*, tetra-*n*-butylammonium perchlorate, nitrate, and bromide. All these salts show a weakly accelerative effect, even the bromide, which would, of course, be a common-ion salt for reactions of methyl bromide, were an S_N1-type mechanism in operation. The results are in Table 3.

Effect of molecular addenda in various concentrations on the second-order rate-constants, k_2, of reaction of methyl bromide with pyridine in benzene at 100°. (The curves are drawn strictly through the experimental points, but the points themselves are not shown, because so many of them are very nearly coincident.)



The accelerations are approximately linear at the salt concentrations employed, but because of the small magnitude of the effects, only a limited significance can be attached to the observed linearity. However, the figures convey no suggestion of a dependence of the accelerations on the square-root of salt concentration (cf. Part LVI).

TABLE 4. *Effect of added salts on the second-order rate-constants (k_2 in sec.$^{-1}$ mole^{-1} l.) of reaction of methyl bromide with pyridine in benzene at* 100°.

(Initial concns. as in Table 2.)

	$Bu^n_4NClO_4$		$Bu^n_4NNO_3$		Bu^n_4NBr	
[Salt]	Run	10^4k_2	Run	10^4k_2	Run	10^4k_2
0·0001	—	—	32	4·70	—	—
0·001	52	4·80	33	4·75	—	—
0·005	51	5·00	34	4·85	53	4·80
0·01	37, 50	5·35	35	5·05	54	4·90

Run 39:	0·005M-$Bu^n_4NClO_4$	+ 0·005M-$Bu^n_4NNO_3$	10^4k_2 = 5·20
„ 38:	0·01M „	+ 0·001M „	„ 5·40
„ 56:	0·005M „	+ 0·001M-Bu^n_4NBr	„ 5·02
„ 55:	„ „	+ 0·005M „	„ 5·10
„ 57:	„ „	+ 0·010M „	„ 5·20

The largest of these kinetic effects is that of the perchlorate; but it is much smaller than any of the effects which this salt produces in the reactions of triphenylmethyl chloride with alcohols. Thus a concentration of 10^{-3}M, which increases the rate of the triphenylmethyl chloride reactions by ratios up to 20-fold, does not increase that of the methyl

bromide reaction by more than 2%. The effects of the nitrate and bromide are successively smaller still. Whereas in the reactions of triphenylmethyl chloride with alcohols, the introduction of tetra-*n*-butylammonium perchlorate, together with tetra-*n*-butylammonium nitrate (or together with any second salt which, when alone, has a weaker catalytic effect than the perchlorate), leads to a smaller rate than the perchlorate alone would have given, the joint effect of tetra-*n*-butylammonium perchlorate and nitrate on the reaction of methyl bromide with pyridine seems to be approximately additive.

The great contrast between the present salt effects, and those described in the preceding papers for reactions of triphenylmethyl chloride, is consistent with the basic difference of mechanism which the author assumes. There are far too few simple ions in benzene appreciably to affect the energy of a bimolecular transition state, and the weak, approximately linear, approximately additive, effects which one does observe seem best ascribed to a macroscopic medium effect of the salts in their stable ion-pair forms.

(2) *Effects of Alkyl Structure on Rates of Menschutkin Reactions : Comparison with Finkelstein Substitutions.*—The second-order rate-constant here given for the reaction of methyl bromide with pyridine at 100° in benzene, $4{\cdot}70 \times 10^{-4}$ sec.$^{-1}$ mole^{-1} l., is in satisfactory agreement with that obtained by Swain and Eddy, *viz.*, $(4{\cdot}82 \pm 0{\cdot}25) \times 10^{-4}$ sec.$^{-1}$ mole^{-1} l. Now Winkler and Hinshelwood [3] have determined rate-constants for the reactions of ethyl and *n*-propyl bromide in benzene at the same temperature. Their data permit the following structural comparison of $10^4 k_2$ values for these Menschutkin reactions: MeBr, 4·70 (100·0°); EtBr, 0·249 (99·8°); Pr^{n}Br, 0·101 (99·7°). The rate-ratio Me : Et is thus about 20 : 1, and the ratio Et : Pr^n is about 2·5 : 1.

Since the present conclusion is that these reactions are bimolecular, it is legitimate to compare the above ratios with those obtained by de la Mare, Fowden, Hughes, Ingold, and Mackie [4] for the bimolecular Finkelstein substitutions of the same alkyl bromides in acetone. The point of the comparison is that the rates of the latter group of S_N2 reactions were analysed, practically and theoretically, with considerable quantitative success, for their polar and steric, energetic and entropic, factors. For example, entropies of transition states were calculated on the assumption that these were bimolecular, with results which agreed well with experiment, but which would be completely upset if in fact the transition states were termolecular.

Table 5 shows the comparison, for the two groups of reaction, not only of the rate-ratios, but also of the corresponding differences, $\Delta G^{\ddagger}$, in the free-energy of activation, and, where possible, the differences in the enthalpic and entropic components $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ of the free-energy, the former component being identified, as an approximation, with the Arrhenius energy of activation, ΔE_A.

TABLE 5. *Rate-ratios and activation-energy differences, for some nucleophilic substitutions of simple alkyl bromides at* 100°.

Substituting agent	Rate-ratios		Activation energy terms (kcal./mole) Diff. (Et − Me)			Diff. (Pr^n − Et)		
	Me : Et	Et : Pr^n	$\Delta H^{\ddagger}$	$-T\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta H^{\ddagger}$	$-T\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$
C_5H_5N	20	2·5	—	—	2·2	0·3	0·4	0·7
Cl^-	34	1·6	1·9	0·7	2·6	0·1	0·4	0·5
Br^-	32	2·0	1·7	0·9	2·6	0·0	0·5	0·5
I^-	72	1·4	2·5	0·7	3·2	−0·1	0·4	0·3

In the above-mentioned analysis of the kinetics of the Finkelstein substitutions, it was shown that, on passing from methyl to ethyl bromide the major part of the decrease in rate is derived from an increase in $\Delta H^{\ddagger}$, which in turn arises as the sum of comparable polar and steric energy contributions; whilst a minor, but still important, part of the rate decrease arises from an increase in $-T\Delta S^{\ddagger}$, which itself is the sum of a minor steric and a major ponderal entropy contribution. It was shown further that, on passing from ethyl

[3] Winkler and Hinshelwood, *J.*, 1935, 1147.
[4] de la Mare, Fowden, Hughes, Ingold, and Mackie, *J.*, 1955, 3169 *et seq.* (8 papers).

to *n*-propyl bromide, there should theoretically be scarcely any increase in $\Delta H^{\ddagger}$, as was not inconsistent with the observations, having regard to the accuracy of the relevant experiments; so that practically the whole of this rate decrease was to be ascribed to the increase in $-T\Delta S^{\ddagger}$, which, in turn, had a negligible steric component, and arose almost wholly from the ponderal entropic effect. Although kinetic analysis of the Menschutkin reactions has not yet been carried as far as that of the Finkelstein substitutions, it does seem almost certain, from the figures in Table 5, that such an analysis of the former group of reactions would give very similar results.

It seems equally clear that the Finkelstein and Menschutkin substitutions are similar in mechanism, and that, since a quantitative treatment of the kinetics of the former confirms their bimolecular nature, we must infer, in agreement with the conclusion derived from kinetic form and catalysis in Section 1, that the Menschutkin reactions of simple alkyl bromides in benzene are S_N2 substitutions.

Experimental

Materials.—The preparation or purification of most of the substances here used is described in Part LIV. Methyl bromide was purified by passing it as vapour through sulphuric acid wash-towers, and then condensing it with exclusion of moisture. Tetra-*n*-butylammonium bromide, prepared as already described for the iodide (Part LIV), had m. p. 120° (Found: Br, 24·8. Calc. for $C_{16}H_{36}NBr$: Br, 24·8%).

Method.—Sets of sealed tubes, each containing 5 ml. of the reaction mixture, were placed in the thermostat at 100·0°, and, severally, at intervals, were withdrawn and cooled, the first such withdrawal marking the kinetic zero. In the contents of each tube, bromide ion was determined, either by Volhard's method or by potentiometric titration, the two methods giving identical results.

Kinetics.—The solubility of methylpyridinium bromide is not above 0·002M at 100°, and therefore this salt became precipitated early during the runs. However, this seemed to make no difference to the rates of the reactions, which gave good second-order constants. Surface catalysis appears to be small, inasmuch as the rates were not appreciably affected, either by adding initially an excess of solid methylpyridinium bromide, or by packing the reaction tubes with glass wool.

Rate constants were calculated by the integrated formula for an irreversible reaction of second order. The details of some sample runs are given in Table 6.

Table 6. *Illustrative experiments on the reaction of methyl bromide with pyridine, without or with added substances, in benzene at* 100·0°.

[In all the runs recorded in this table, the initial concentration of methyl bromide was 0·12M, and of pyridine 0·20M. The concentrations x of product are in mole l.$^{-1}$, and are reckoned as excesses over the small amounts found at the kinetic time-zero. The times t are in min., and the corresponding integrated rate-constants k_2 are in sec.$^{-1}$ mole^{-1} l.]

Run 2			Run 18			Run 15			Run 35		
Nothing added			[MeOH] = 0·10M			[$PhNO_2$] = 0·20M			[Bu_4NNO_3] = 0·01M		
t	10^2x	10^4k_2	t	10^2x	10^4k_2	t	10^2x	10^4k_2	t	10^2x	10^4k_2
15	0·95	4·69	15	1·05	5·34	15	1·20	6·04	15	1·00	4·96
30	1·80	4·73	30	2·00	5·35	30	2·20	5·97	30	1·92	5·11
60	3·18	4·67	60	3·52	5·35	45	3·10	6·05	60	3·37	5·05
90	4·32	4·68	90	4·70	5·32	60	3·83	5·96	90	4·51	5·00
120	5·25	4·70	120	5·70	5·36	90	5·10	6·00	120	5·48	5·03
150	6·05	4·74	150	6·48	5·35	120	6·14	6·10	150	6·29	5·15
180	6·67	4·69	180	7·12	5·33	150	6·92	6·02	180	6·93	5·05
210	7·27	4·70	210	7·70	5·38	180	7·50	5·91	210	7·48	5·05
240	7·70	4·70	240	8·18	5·38	210	8·07	6·00			

I gratefully acknowledge the considerable help which has been received from Mr. A. Spiers, B.Sc., in the experimental work recorded in this group of papers.

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University College, Gower St., London, W.C.1. [*Received, October 5th*, 1956.]

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242. *Raman Spectrum and Structure of the Hexabromostannate Ion in Aqueous Solution.*

By L. A. Woodward and L. E. Anderson.

Raman spectra are photographed for a range of molar aqueous solutions of stannic bromide containing different concentrations of hydrobromic acid. The spectrum present at low concentrations of acid disappears progressively as the acid concentration is increased and is replaced by a new spectrum consisting of three lines: $\Delta\nu = 185$ cm.$^{-1}$, very strong, polarised; $\Delta\nu = 137$ cm.$^{-1}$, medium strong, depolarised; and $\Delta\nu = 95$ cm.$^{-1}$, medium strong, depolarised. The number of lines, states of polarisation, etc., are as expected for a regular octahedral species XY_6, and the spectrum is attributed to the $SnBr_6^{2-}$ ion. The conclusion of previous workers that this ion has a lower symmetry was evidently due to their assignment to it of all the Raman lines of a solution which must have contained other species.

The hexachlorostannate ($SnCl_6^{2-}$) and the hexabromostannate ($SnBr_6^{2-}$) ion have valency shells of twelve electrons like the hexafluorides of Group VI elements, and so should have the same regular octahedral structure and show the characteristic three-line Raman spectrum. This is true [1,2] for the hexachlorostannate ion, for example in aqueous solutions of stannic chloride containing hydrochloric acid. For a solution of stannic bromide containing hydrobromic acid, on the other hand, Redlich and co-workers [1,3] observed more than three Raman lines, and hence concluded that the hexabromostannate ion must have a shape less highly symmetrical than the regular octahedral: they suggested a configuration (point group D_{4h}) with two polar bromine atoms at a distance from the central tin atom different from that of the four equatorial bromine atoms.

The present investigation is concerned principally with the Raman spectra of a range of solutions of stannic bromide containing different concentrations of hydrobromic acid. The results show that the earlier conclusion about the shape of the hexabromostannate ion is wrong. The previously reported spectrum of the hexachlorostannate ion is confirmed.

Results

Stannic bromide dissolves in aqueous hydrobromic acid with considerable evolution of heat. The temperature was prevented from rising unduly by water-cooling. The freshly prepared solutions varied from practically colourless to deep yellow, according to composition. For a series all containing the same concentration of stannic bromide, the strength of the yellow colour increased with increasing concentration of hydrobromic acid, *i.e.*, with increasing value of the fraction $R = [\text{total Br}]/[\text{Sn}]$. Also for solutions of the same value of R the colour was the stronger, the greater the actual concentration. For instance, with $R = 7$ the range was from nearly colourless for $[SnBr_4] = \frac{1}{2}$M to deep yellow for $[SnBr_4] = 3$M.

The series of solutions investigated by the Raman method were all molar with respect to stannic bromide and had R-values ranging from 4 to 13. For each solution the Raman spectrum was photographed with a series of exposure times. That with $R = 4$ was used immediately after being made up. It remained practically colourless long enough for its spectrum to be obtained both by excitation with the mercury blue line (4358 Å) and with the mercury green line (5461 Å). After a few hours this solution became noticeably yellow, darkening during several weeks until finally a turbidity appeared. The other solutions were all yellow from the start, so that only the green line could be used for excitation of their spectra.

For values of R from 4 to 6 the spectrum consisted of a single, somewhat diffuse line with $\Delta\nu = 220$ cm.$^{-1}$. For these solutions the primary line at 5461 Å also showed a distinct broadening, probably due to an unresolved diffuse Raman band centred at about $\Delta\nu = 80$ cm.$^{-1}$. For the solution with $R = 4$ this band could be more distinctly observed near the mercury blue

[1] Redlich, Kurz, and Rosenfeld, *Z. phys. Chem.*, 1934, *B*, **19**, 231.
[2] Couture and Mathieu, *Compt. rend.*, 1947, **225**, 1140.
[3] Redlich, Kurz, and Stricks, *Monatsh.*, 1937, **71**, 1.

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line, where the dispersion of the spectrograph is greater. At $R = 8$ the line characteristic of lower R-values was still present, though with diminished intensity and slightly shifted to lower $\Delta\nu$, while a new line had made its appearance with $\Delta\nu = 185$ cm.$^{-1}$. As R was further increased, the first line (as also the apparent broadening of the primary line) disappeared progressively, while at the same time the new line increased in intensity along with two other new and somewhat less intense companions ($\Delta\nu = 138$ and 95 cm.$^{-1}$). At values of R above about 11 these three new lines were the sole features of the Raman spectrum. The one of highest $\Delta\nu$ and greatest intensity was found to be highly polarised, the other two to be depolarised. The experimental results for the typical solutions with $R = 4$, 8, and 13 are given in Table 1. For strong sharp lines the estimated limits of error of the measured $\Delta\nu$-values are ± 3 cm.$^{-1}$; but for weaker or more diffuse lines the errors may be larger.

TABLE 1. *Raman spectra of molar aqueous solutions of stannic bromide containing different concentrations of hydrobromic acid.*

R	Colour	Exciting line (Å)	$\Delta\nu$ (cm.$^{-1}$) Stokes	Anti-Stokes	Description
4	colourless (fresh)	4358	218	221	strong, polarised
			~80	—	weak, broad
8	yellow	5461	209	209	medium, polarised
			184	187	medium, polarised
			140	139	weak, depolarised
			101	102	weak, depolarised
13	deep yellow	5461	185	185	very strong, polarised
			139	136	medium, depolarised
			96	94	medium, depolarised

For comparison, several 2M-solutions of stannic chloride in hydrochloric acid ($R = 4$—9) were similarly examined. Used immediately after preparation, all were clear and colourless, so that their spectra could be excited by the mercury blue line. All gave identical spectra consisting of three lines: $\Delta\nu = 311$ cm.$^{-1}$, strong, polarised; $\Delta\nu = 229$ cm.$^{-1}$, medium weak, depolarised; and $\Delta\nu = 158$ cm.$^{-1}$, medium strong, depolarised.

DISCUSSION

The colours of solutions of stannic bromide containing hydrobromic acid clearly indicate that at least two species are involved, one colourless and the other deep yellow. The equilibrium between them is shifted in favour of the latter by increase of bromide-ion concentration relative to that of tin or by increase of the concentration of the solution as a whole. These facts are consistent with the view that the colourless species might be $SnBr_4$ and that the yellow one is $SnBr_6^{2-}$, the equilibrium being $SnBr_4 + 2Br^- \rightleftharpoons SnBr_6^{2-}$. The possibility is not excluded, however, that other colourless species might be involved.

The Raman spectra (see Table 1) show that the line at $\Delta\nu = 220$ cm.$^{-1}$ characterises the colourless species at low R-values; and it is interesting to note that this frequency is identical with that of the most intense line of pure stannic bromide (Class A_1, polarised), as given by Herzberg.[4] The band centred at about $\Delta\nu = 80$ cm.$^{-1}$ is also near the positions of $\nu_2(E)$ and $\nu_4(F_2)$ of $SnBr_4$ (64 and 88 cm.$^{-1}$, respectively). The exact nature of the colourless species must remain uncertain; but there seems to be no doubt that the yellow species must be the hexabromostannate ion, $SnBr_6^{2-}$. Its three-line spectrum, alone present at sufficiently high values of [total Br]/[Sn], is precisely of the kind characteristic of a regular octahedral species (point group O_h) of type XY_6. We can confidently assign the observed frequencies as follows: ν_1 (A_{1g}) = 185 cm.$^{-1}$; ν_2 (E_g) = 138 cm.$^{-1}$; and ν_5 (F_{2g}) = 95 cm.$^{-1}$.

It is clear that the erroneous conclusion of previous workers [1,3] that $SnBr_6^{2-}$ must have a lower symmetry (such as D_{4h}), was based upon their assignment to this ion of all the Raman lines of a solution which must have contained the colourless species as well. The composition of their solution was not specified exactly. Their observed frequencies (208, 183, 142, 102, and 72 cm.$^{-1}$) agree quite well with what we have observed for the

[4] Herzberg, "Infrared and Raman Spectra," Van Nostrand, New York, 1945, p. 167.

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solution with $R = 8$, if we identify their $\Delta\nu = 72$ cm.$^{-1}$ with the band centred at approximately 80 cm.$^{-1}$ observed by us at $R = 4$ (see Table 1).

For the undoubtedly regular octahedral $SnCl_6^{2-}$ ion our observed frequencies agree satisfactorily with those of earlier workers,[1,2,5] and are clearly to be assigned as $\nu_1 = 311$, $\nu_2 = 229$, and $\nu_5 = 158$ cm.$^{-1}$. The difference of behaviour of solutions of stannic chloride, as compared with solutions of stannic bromide, is noteworthy. Even in absence of hydrochloric acid a freshly prepared solution of the chloride shows [5] the Raman lines of $SnCl_6^{2-}$ ions, due presumably to some reaction such as $3SnCl_4 = Sn^{4+} + 2SnCl_6^{2-}$. With stannic bromide, however, a considerable excess of bromide ions is necessary in order to obtain an appreciable proportion of $SnBr_6^{2-}$ ions.

Table 2 shows a comparison of the totally symmetric, purely bond-stretching vibrational frequencies of the $SnCl_6^{2-}$ and $SnBr_6^{2-}$ ions with those of the corresponding neutral tetra-

TABLE 2. *Totally symmetric frequencies and force constants.*

Species	ν_1 (cm.$^{-1}$)	$10^{-5}k$ (dynes/cm.)	Force const. ratio	Species	ν_1 (cm.$^{-1}$)	$10^{-5}k$ (dynes/cm.)	Force const. ratio
$SnCl_4$	366	2·80	1·39	$SnBr_4$ ...	220	2·28	1·42
$SnCl_6^{2-}$ ...	311	2·02		$SnBr_6^{2-}$...	185	1·61	

halide molecules.[4] The stretching force constants, k, calculated by the simple valency force field, are also compared. The fact that the force-constant ratio is practically the same for the bromo- and the chloro-species provides evidence that we are correct in attributing to the $SnBr_6^{2-}$ ion the spectrum observed for the bromide solutions at high values of R.

EXPERIMENTAL

The Raman light source was a low-pressure mercury arc lamp with water-cooled electrodes (Toronto arc). The states of polarisation of the Raman lines were determined qualitatively by the method of polarised incident light, successive exposures being taken with cylinders of suitably oriented Polaroid surrounding the Raman vessel. The spectrograph was a 2-prism glass instrument with f/5·6 camera, giving dispersions of about 200 cm.$^{-1}$/mm. in the region of the mercury blue line (4358 Å) and about 300 cm.$^{-1}$/mm. in the region of the green line (5461 Å). The plates used were Kodak Special Scientific, emulsion type Oa, sensitivity G. Exposure times were of ½—3 hr., without Polaroid.

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[5] Guèron, *Ann. Chim.*, 1935, **3**, 305.

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243. *Alicyclic Studies. Part IV.** 11-*Oxo*cyclo*hepta*[a]*naphthalene.*

By DOV ELAD and DAVID GINSBURG.

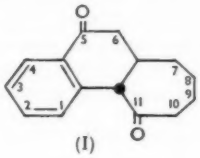
The synthesis of 11-oxo*cyclo*hepta[*a*]naphthalene (II) from an alicyclic intermediate is described.

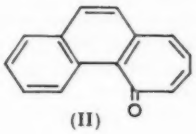
THE synthesis [1] of the *trans*-compound (I) made available a starting material for the preparation of 11-oxo*cyclo*hepta[*a*]naphthalene (II). There have been conflicting reports as to the ability of dibenzo[*a*, *e*]*cyclo*heptatrienone (III) to form ketonic derivatives [2,3,4] but it seems clear that it forms a 2 : 4-dinitrophenylhydrazone in contradistinction to the behaviour of tropone [5] itself, owing to the absence of coplanarity in the tricyclic compound (III). Examination of models indicates that the analogue (II) is coplanar and thus might be expected to exhibit behaviour more analogous to that of tropone.

* Part III, *J.*, 1954, 2955.

[1] Ginsburg and Pappo, *J. Amer. Chem. Soc.*, 1953, **75**, 1094.
[2] Bergmann, Fischer, Ginsburg, Hirshberg, Lavie, Mayot, Pullman, and Pullman, *Bull. Soc. chim. France*, 1951, **18**, 684.
[3] Buchanan, *Chem. and Ind.*, 1952, 855.
[4] Bergmann and Ginsburg, *ibid.*, 1954, 45.
[5] Doering and Detert, *J. Amer. Chem. Soc.*, 1951, **73**, 876.

Catalytic reduction of the diketone (I) removed the carbonyl group conjugated to the aromatic nuceleus and stepwise bromination and dehydrobromination afforded the naphthalenic ketone (IV). Although treatment of this with *n*-pentyl nitrite and sodium ethoxide afforded the α-hydroxyimino-ketone which in turn was converted through acid hydrolysis into the (enolised) α-diketone (V), all attempts to introduce an additional double bond in order to form the corresponding naphthotropolone failed.


(I)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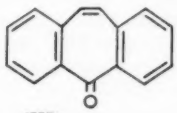
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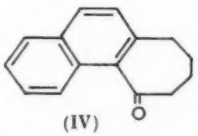
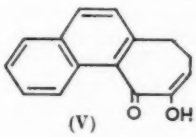

(IV)


(V)

However, stepwise bromination and dehydrobromination of the tetrahydro-ketone (IV) afforded the desired compound (II). No ketonic derivative could be prepared but a very unstable and hygroscopic picrate was formed which could not be characterised in pure form.

Experimental

Infrared and ultraviolet spectra were measured in $CHCl_3$ and MeOH, respectively.

6 : 6a : 7 : 8 : 9 : 10 : 11 : 11a-*Octahydro*-11-*oxo*-5H-cyclo*hepta*[a]*naphthalene*.—The diketone (I) (12 g.) was hydrogenated in acetic acid (150 ml.) in the presence of 10% palladised charcoal (1·2 g.) at 60—70° at an initial hydrogen pressure of 60 lbs./sq. in. Hydrogen uptake ceased after 3 hr. The catalyst was filtered off, the solvent was removed by distillation, and the residue was distilled in a high vacuum. The first fraction (9·5 g.) consisted of the desired *ketone*, b. p. 160—162°/1·5 mm. The higher-boiling fraction (1·5 g.) was recovered diketone, b. p. 177—180°/0·7 mm. The product crystallised very slowly and had m. p. 80—81·5° (from ethanol) (Found: C, 83·7; H, 8·8. $C_{15}H_{18}O$ requires C, 84·1; H, 8·5%). Infrared absorption: 1703 cm.$^{-1}$ (C=O). Ultraviolet absorption: 2660, 2810—2850 Å (log ε 2·79, 2·30).

The *oxime* formed colourless needles, m. p. 145—147° (from aqueous ethanol) (Found: C, 78·5; H, 8·3; N, 6·2. $C_{15}H_{19}ON$ requires C, 78·6; H, 8·35; N, 6·1%). Ultraviolet absorption: 2660 Å (log ε 3·57).

6 : 7 : 8 : 9 : 10 : 11-*Hexahydro*-11-*oxo*cyclo*hepta*[a]*naphthalene*.—A mixture of the above ketone (710 mg., 0·003 mole), *N*-bromosuccinimide (650 mg., 0·0033 mole), carbon tetrachloride (15 ml.), and several crystals of dibenzoyl peroxide was heated under reflux, soon becoming pale orange. The colour suddenly disappeared after a few minutes. After 30 min. of boiling all of the heavy brominating agent had been converted into succinimide which floated on the surface. Some hydrogen bromide evolution was observed. The succinimide was removed by filtration, and the solvent under reduced pressure. Attempts to crystallise the residue failed. 2 : 6-Lutidine (15 ml.) was added to the residue and the mixture was refluxed for 2 hr. After the usual working up [6] the αβ-unsaturated ketone was obtained as an oil (690 mg.), b. p. 161—163°/0·5 mm. Infrared absorption: 1685 cm.$^{-1}$ (C=O). This was characterised as the *oxime*, needles, m. p. 143—145° (from aqueous methanol) (admixture with the oxime of the starting material gave a depression to 120—126°) (Found: C, 78·9; H, 7·7; N, 6·4. $C_{15}H_{17}ON$ requires C, 79·3; H, 7·5; N, 6·2%). Ultraviolet absorption: 2240, 2670 Å (log ε 3·26, 2·39).

When larger quantities (5—10 g.) of ketone were brominated, the reaction was exothermic and was complete in 10—15 min.

6 : 7 : 8 : 9-*Tetrahydro*-11-*oxo*cyclo*hepta*[a]*naphthalene*.—The αβ-ethylenic ketone (3·55 g.)

[6] Elad and Ginsburg, *J.*, 1954, 471.

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after bromination with *N*-bromosuccinimide as above (1·5 hr. to complete reaction) and dehydrobromination with 2 : 6-lutidine gave the naphthalenic *ketone* (IV) (2·84 g.), b. p. 178—182°/1·1 mm. Infrared absorption : 1675 cm.$^{-1}$ (C=O). The *oxime* formed needles, m. p. 158—160° (from aqueous ethanol) (Found : C, 79·85; H, 6·7; N, 6·2. $C_{15}H_{15}ON$ requires C, 80·0; H, 6·7; N, 6·2%). Ultraviolet absorption : 2270, 2870 Å (log ε 4·73, 3·71).

6 : 7 : 8 : 9-*Tetrahydro*-10-*hydroxyimino*-11-*oxo*cyclo*hepta*[a]*naphthalene*.—To a solution of sodium ethoxide [from 115 mg. (0·005 mole) of sodium and 3 ml. of ethanol] was added a solution of the ketone (IV) (1·05 g., 0·005 mole) in ethanol (5 ml.). *n*-Pentyl nitrite (0·69 ml.) was added to the ice-cold solution and the homogeneous solution was left at 0° for 24 hr. Ether, water, and acetic acid (1 ml.) were added and the aqueous phase was extracted with several portions of ether. The combined ether solutions were extracted with Claisen's alkali. Acidification of the latter with acetic acid precipitated an oil which crystallised. The *hydroxyimino-ketone* (0·8 g.) was triturated with methanol and had m. p. 169—171° (decomp.). Recrystallisation from ethanol yielded a sample, m. p. 183—185° (decomp.) (Found : C, 75·6; H, 5·3; N, 5·8. $C_{15}H_{13}O_2N$ requires C, 75·3; H, 5·5; N, 5·85%). A dioxan solution of this substance gives a green colour with alcoholic ferric chloride.

α-*Phenyltropolone*.—A mixture of 2-phenyl*cyclo*hept-2-enone [1] (0·93 g., 0·005 mole), dioxan (40 ml.), and selenium dioxide (0·62 g., 0·0055 mole) was refluxed for 4·5 hr. The precipitated selenium was filtered off and the dioxan was removed under reduced pressure. The residue was dissolved in ether and was washed many times with dilute silver nitrate solution and then with water. Evaporation of the ether gave an oil (850 mg.) which gave a green colour with alcoholic ferric chloride. This residue was refluxed in 1 : 2 : 4-trichlorobenzene (15 ml.) with 10% palladised charcoal (1·5 g.) for 5 hr. under nitrogen. After cooling and dilution with benzene, the solution was washed with sodium carbonate solution and with 2N-sodium hydroxide. The emulsion was destroyed with ether. Acidification of the alkaline extracts, and chloroform extraction, followed by removal of the solvent, gave a residue (60 mg.). Treatment with boiling hexane gave a solution which on concentration deposited α-phenyltropolone, m. p. 116—116·5° (from hexane). Doering and Mayer [7] report m. p. 116—116·5° and the infrared and ultraviolet absorption spectra which they report are superimposable on those of our product.

8 : 9-*Dihydro*-10-*hydroxy*-11-*oxo*cyclo*hepta*[a]*naphthalene*.—To a solution of the hydroxyiminoketone (0·5 g.) and sodium nitrite (1·2 g.) in 1 : 1 aqueous methanol (200 ml.) was added with stirring and cooling concentrated sulphuric acid (1·2 ml.). The solution was kept at 35—40° for 36 hr. with occasional stirring to dissolve the solid. Finally, a yellow homogeneous solution was obtained. The pH was adjusted to 6 by means of aqueous sodium carbonate. The mixture was concentrated under reduced pressure to about one-half of its original volume (bath-temp. 60°). The oil which was precipitated was taken up in ether, and the extract was washed with water. The residue obtained on evaporation of the ether (450 mg.) gave a dark brown colour with alcoholic ferric chloride and contained no nitrogen. Infrared absorption : 1684 cm.$^{-1}$ (C=O). It was characterised as the red 2 : 4-*dinitrophenylhydrazone*, m. p. 259·5—260·5° (from chloroform–ethanol) (Found : C, 62·75; H, 3·6; N, 13·9. $C_{21}H_{16}O_5N_4$ requires C, 62·4; H, 4·0; N, 13·9%). Attempts to dehydrogenate this substance to the tropolone, including treatment as described above for the preparation of α-phenyltropolone, failed.

Bromination Experiments towards Synthesis of 11-*Oxo*cyclo*hepta*[a]*naphthalene*.—(*a*) To a solution of the ketone (IV) (2·1 g., 0·01 mole) in carbon tetrachloride (10 ml.) was added at room temperature bromine (1·1 ml., 0·02 mole) in carbon tetrachloride (4 ml.). The solution was kept for 1 hr. with occasional shaking. The colour disappeared after the solution had been heated on the steam-bath for an additional 10 min. Removal of the solvent under reduced pressure gave a solid residue, whence trituration with hexane yielded the crystalline 6 : 6-*dibromo-compound* [8] (2 g.), m. p. 144—146° (from hexane). Concentration of the hexane solution gave further crops (0·4 g.) (Found : Br, 43·8. $C_{15}H_{12}OBr_2$ requires Br, 43·5%). Infrared absorption : 1707 cm.$^{-1}$ (C=O).

(*b*) A mixture of the dibromo-ketone (1 g.), tributylamine (8 ml.), and tetralin (25 ml.) was refluxed for 12 hr.[8] The precipitate of tributylamine hydrobromide was filtered off and the solvents were removed under reduced pressure. The oily residue was dissolved in ether and washed with dilute hydrochloric acid and with water. Evaporation yielded the 6-*bromo*-$\Delta^{6(7)}$-*ketone* as an oil (Found : Br, 27·0. $C_{15}H_{11}OBr$ requires C, 27·5%).

[7] Doering and Mayer, *J. Amer. Chem. Soc.*, 1953, **75**, 2387.
[8] Cf. Lyle and Covery, *J. Amer. Chem. Soc.*, 1953, **75**, 4973.

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(*c*) To a boiling solution of the ketone (IV) (1·05 g., 0·005 mole) in carbon tetrachloride (10 ml.) was added bromine (0·27 ml., 0·005 mole) in carbon tetrachloride (4 ml.). The bromine colour disappeared at once. Refluxing was continued for 1 hr. Removal of the solvent afforded an oil which was dissolved in ether and washed with aqueous sodium carbonate and with water. Removal of the ether gave the *6-bromo-ketone* as an oil (Found: Br, 27·0. $C_{15}H_{13}OBr$ requires Br, 27·3%).

(*d*) A mixture of the 6-bromo-ketone (1·45 g., 0·02 mole), *N*-bromosuccinimide (0·84 g., 0·02 mole), carbon tetrachloride (15 ml.), and several crystals of dibenzoyl peroxide was refluxed for 2·5 hr. Some evolution of hydrogen bromide was observed. After removal of the succinimide and the solvent, the oily residue could not be induced to crystallise. Seeding with the crystalline 6 : 6-dibromo-ketone did not induce crystallisation. The residue is therefore believed to be partially dehydrobrominated 6 : 9-dibromo-ketone since the analytical value for bromine was low (Found: Br, 38·3. Calc. for $C_{15}H_{12}OBr_2$: Br, 43·8. Calc. for $C_{15}H_{13}OBr$: Br, 27·3%).

The residue was treated with collidine (20 ml.) and the mixture was heated on the steam-bath for 1 hr. The solvent was removed under reduced pressure, ether and water were added, and the ether solution was washed with dilute hydrochloric acid, dilute sodium hydrogen carbonate solution, and with water and dried (Na_2SO_4). Evaporation of the ether and evaporative distillation of the residue (bath, 190°/0·1 mm.) yielded the colourless *tropone* (II) (0·4 g.) as a slightly yellow oil (Found: C, 87·5; H, 4·75. $C_{14}H_{10}O$ requires C, 87·35; H, 4·9%). No ketonic derivatives could be prepared; a yellow-orange picrate, m. p. 116—121° (sealed tube), was obtained but could not be analysed.

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ISRAEL INSTITUTE OF TECHNOLOGY, HAIFA, ISRAEL. [*Received, September 24th*, 1956.]

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244. *Alicyclic Studies. Part V.* The Preparation of 2-Naphthylcycloalk-2-enones.*

By RIVKA BAR-SHAI and DAVID GINSBURG.

2-α-Naphthyl- and 2-β-naphthyl-*cyclo*pent-2-enone and 2-β-naphthyl*cyclo*hept-2-enone have been prepared from the corresponding 1-naphthyl*cyclo*alkenes through the nitrosochlorides and oximes.

2-ARYL*cyclo*HEX-2-ENONES,[1] 2-phenyl*cyclo*pent-2-enone,[2] and 2-phenyl*cyclo*hept-2-enone [3] have been prepared from the corresponding 1-aryl*cyclo*alkenes. This method of preparation has now been extended to 1-naphthyl*cyclo*alkenes. The use of 1-α- and 1-β-naphthyl-*cyclo*hexene as starting materials for preparation of the corresponding αβ-ethylenic ketones as intermediates in the synthesis of 3 : 4-benzophenanthrene and chrysene, respectively, is being described elsewhere.[4,5] In this communication, the analogous preparation of 2-α- and 2-β-naphthyl*cyclo*pent-2-enone and 2-β-naphthyl*cyclo*hept-2-enone as intermediates for the preparation of various tetracyclic systems is described.

EXPERIMENTAL

1-α-Naphthyl*cyclo*pentene was prepared by the method of Bachmann and Kloetzel [6] in 46% yield.

2-α-*Naphthyl*cyclo*pent-2-enone Oxime*.—(*a*) The nitrosochloride of the above *cyclo*alkene was prepared by dropwise addition of concentrated hydrochloric acid (5 ml.) to a vigorously stirred mixture of the hydrocarbon (5 g.), *n*-pentyl nitrite (7 ml.), and glacial acetic acid (10 ml.) at −10° to −7°.

(*b*) The crystalline nitrosochloride was removed and added without purification to pyridine

* Part IV, preceding paper.

[1] Ginsburg and Pappo, *J.*, 1951, 516.
[2] Amiel, Loeffler, and Ginsburg, *J. Amer. Chem. Soc.*, 1954, **76**, 3625.
[3] Ginsburg and Pappo, *ibid.*, 1953, **75**, 1094.
[4] Klibansky and Ginsburg, *J.*, 1957, 1293.
[5] *Idem, ibid.*, p. 1299.
[6] Bachmann and Kloetzel, *J. Amer. Chem. Soc.*, 1938, **60**, 2204.

(40 ml.). The mixture was warmed on a steam-bath for 15 min. The solid dissolved and the brown solution was diluted with cold water (100 ml.). Crystallisation of the precipitated oil was induced by scratching. Filtration yielded the crude *oxime*. The analytical sample obtained by recrystallisation from benzene had m. p. 208—210° (1·9 g.) (Found: C, 80·6; H, 5·8; N, 6·25. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·9; N, 6·3%).

2-α-*Naphthyl*cyclo*pent*-2-*enone*.—The oxime (1 g.) was hydrolysed by refluxing it with concentrated hydrochloric acid (2 ml.) and water (30 ml.) for 4 hr. The *ketone*, recrystallised from *cyclo*hexane, had m. p. 110—112° (0·8 g.) (Found: C, 86·6; H, 5·7. $C_{15}H_{12}O$ requires C, 86·5; H, 5·8%). Infrared absorption (C=O): 1700 cm.$^{-1}$. The orange-red 2:4-*dinitrophenylhydrazone* obtained in the usual way had m. p. 248—250° (from ethanol–ethyl acetate) (Found: C, 65·1; H, 4·0; N, 14·45. $C_{21}H_{16}O_4N_4$ requires C, 64·9; H, 4·15; N, 14·4%).

2-α-*Naphthyl*cyclo*pentanone*.—Hydrogenation of the αβ-ethylenic ketone (0·5 g.) in ethyl acetate with 10% palladised carbon (0·2 g.) during 1 hr. yielded the saturated ketone, m. p. 92—93° (methanol). The orange 2:4-dinitrophenylhydrazone had m. p. 213—214° (from acetonitrile). Klemm and Ziffer [7] report m. p. 91—93° and 212·5—213·5°, respectively, for these compounds.

1-β-*Naphthyl*cyclo*pentanol*.—*n*-Butyl-lithium was prepared in the usual way [8] from lithium wire (5·5 g.) and *n*-butyl bromide (43 g.) in dry ether (200 ml.). The solution was filtered under nitrogen and a solution of β-bromonaphthalene (50 g.) in dry ether (100 ml.) was added during 1 hr. under nitrogen at room temperature. The mixture was stirred for an additional 30 min., then cooled to −10°, and a solution of *cyclo*pentanone (20 g.) in dry ether (40 ml.) was added dropwise at < −5°. The temperature was permitted to rise slowly and the mixture kept overnight. It was decomposed with saturated ammonium chloride solution and the ether was removed. The *alcohol* solidified and, recrystallised from hexane, had m. p. 83—85° (25 g.), infrared absorption (OH) at 3590 cm.$^{-1}$ (Found: C, 84·95; H, 7·5. $C_{15}H_{16}O$ requires C, 84·9; H, 7·6%).

1-β-*Naphthyl*cyclo*pentene*.—The above alcohol (25 g.) was boiled with anhydrous oxalic acid (6 g.) in toluene (150 ml.), until the theoretical quantity of water was removed azeotropically. After the usual working up [1] the *cyclo*alkene was obtained by distillation. It had b. p. 141°/0·6 mm., m. p. 84—85° (ethanol) (20 g.). Bachmann and Kloetzel [6] report m. p. 84—85°. Admixture with the alcohol gave a large m. p. depression.

2-β-*Naphthyl*cyclo*pent*-2-*enone Oxime*.—(*a*) The nitrosochloride could not be prepared from the *cyclo*alkene owing to sparing solubility of the latter in acetic acid. It was therefore prepared directly from the alcohol. Concentrated hydrochloric acid (6 ml.) was added dropwise at −5° to 0° to a vigorously stirred mixture of the alcohol (5 g.), *n*-pentyl nitrite (7 ml.), and glacial acetic acid (20 ml.). The mixture was stirred for an additional 2 hr. and the nitrosochloride was filtered off and washed with cold methanol. (*b*) The crude nitrosochloride was treated as described above for its isomer. The *oxime*, recrystallised from benzene, had m. p. 181—182° (1·9 g.) (Found: C, 80·7; H, 6·0; N, 6·1%).

2-β-*Naphthyl*cyclo*pent*-2-*enone*.—Hydrolysis of the oxime (0·5 g.) was carried out as described above for its isomer. The crude ketone was extracted with ether, the solvent removed, and the residue was distilled, giving the *ketone* b. p. 157—158°/0·02 mm., m. p. 103—104° (from hexane) (0·4 g.) (Found: C, 86·0; H, 5·7%). Infrared absorption (C=O): 1700 cm.$^{-1}$. The red 2:4-*dinitrophenylhydrazone* had m. p. 254—255° (from nitromethane) (Found: C, 64·8; H, 4·0; N, 14·6%). The colourless *semicarbazone* had m. p. 220—222° (from ethanol) (Found: C, 72·0; H, 5·75; N, 15·4. $C_{16}H_{15}ON_3$ requires C, 72·4; H, 5·7; N, 15·8%).

2-β-Naphthyl*cyclo*pentanone, obtained by reduction as described above for its isomer, had m. p. 80—81°. Its orange 2:4-dinitrophenylhydrazone had m. p. 163—164°. Klemm and Ziffer [7] report m. p.s 80—83° and 162—163°, respectively.

1-β-*Naphthyl*cyclo*heptene*.—This was prepared on the same scale as described for 1-β-naphthyl*cyclo*pentene from *n*-butyl-lithium and *cyclo*heptanone (27 g.). Dehydration of the crude mixture of alcohol (partially dehydrated even by ammonium chloride) and *cyclo*alkene was completed by refluxing with oxalic acid in toluene. The *cyclo*alkene distilled at 147°/0·35 mm. and appeared to have m. p. *ca.* 20° (27 g.).

2-β-*Naphthyl*cyclo*hept*-2-*enone Oxime*.—This was prepared as above. It did not crystallise and was therefore taken up in ether and extracted with Claisen's alkali. After acidification of

[7] Klemm and Ziffer, *J. Org. Chem.*, 1956, **21**, 274.
[8] Gilman, Beel, Brannen, Bullock, Dunn, and Miller, *J. Amer. Chem. Soc.*, 1949, **71**, 1499.

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the latter extract the oxime was taken up in chloroform, and the solvent was removed. Attempted vacuum-distillation of the oxime was unsuccessful as the crude oxime largely decomposed to give polymeric material. A small amount of material (0·3 g.) was obtained having b. p. 200—206°/0·1 mm., m. p. 185° (from pentane).

2-β-*Naphthyl*cyclo*hept*-2-*enone*.—This ketone was obtained by hydrolysis of the crude undistilled oxime (5 g.) with boiling 10% hydrochloric acid for 15 hr. Chloroform-extraction yielded the crude oily ketone (3 g.) [infrared absorption (C=O) : 1685 cm.$^{-1}$], characterised as the orange-red 2 : 4-*dinitrophenylhydrazone*, m. p. 125° (from nitromethane) (Found : C, 66·35; H, 4·8; N, 13·5. $C_{23}H_{20}O_4N_4$ requires C, 66·3; H, 4·8; N, 13·5%).

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245. *Alicyclic Studies. Part VI.* The Synthesis of 2-Phenylcycloöct-2-enone.*

By Th. Weil and David Ginsburg.

2-Phenyl*cyclo*oct-2-enone has been prepared from 1-phenyl*cyclo*octene *via* the nitrosochloride and the oxime.

2-Phenyl*cyclo*oct-2-enone was required as an intermediate for the synthesis of a tricyclic analogue of phenanthrene in which one benzenoid ring is replaced by a *cyclo*octatetraene ring. Its synthesis followed the preparation of other 2-aryl*cyclo*alk-2-enones.[1]

1-Phenyl*cyclo*octene nitrosochloride was prepared directly from 1-phenyl*cyclo*octan-1-ol which undergoes dehydration under the conditions of this reaction or from 1-phenyl*cyclo*octene. In this case a base stronger than pyridine is required for the dehydrochlorination. Alcoholic potassium hydroxide was used to convert the nitrosochloride into the oxime of the required αβ-ethylenic ketone. Acidic hydrolysis of the oxime yielded the ketone. Proof of its structure was obtained by reduction to 2-phenyl*cyclo*octanone.[2]

Since 40% hydrogen peroxide was not available to us, the authentic specimen of 2-phenyl*cyclo*octanone had to be prepared by a modification of Cope and Smith's method [2] in which 30% hydrogen peroxide was substituted. The infrared absorption of the mixture obtained after the epoxidation step and acid treatment showed that it contained the allylic alcohol and acetate as stated [2] but that clearly 2-phenyl*cyclo*octanone was also present in high concentration. Therefore, 2 : 4-dinitrophenylhydrazine solution was added and immediate precipitation of the 2 : 4-dinitrophenylhydrazone of 2-phenyl*cyclo*octanone occurred. This product was identical with that subsequently obtained by following explicitly the complete synthetic procedure suggested by Cope and Smith.[2]

A crystalline by-product was usually obtained during the hydrolysis of 2-phenyl*cyclo*oct-2-enone oxime. This was identified as ω-benzoylheptanoic acid and was presumably formed by partial Beckmann rearrangement of the αβ-ethylenic oxime to a nine-membered unsaturated lactam which upon further hydrolysis to the amino-acid containing a vinylamine function finally gave the keto-acid. Its structure was proved by oxidation of 1-phenyl*cyclo*octan-1-ol which yielded ω-benzoylheptanoic acid identical with the above by-product.

Experimental

1-*Phenyl*cyclo*octan*-1-*ol*.—*cyclo*Octanone (76·7 g., 0·6 mole) was added dropwise with stirring at 0° to a Grignard reagent prepared from magnesium (19·5 g.) and bromobenzene (125·6 g., 0·8 mole) in dry ether (800 ml.). After refluxing for 1 hr. the mixture was decomposed with ammonium chloride (250 g.) in water (1 l.). The ether layer was separated and the aqueous

* Part V, preceding paper.

[1] Ginsburg and Pappo, *J.*, 1951, 516; *J. Amer. Chem. Soc.*, 1953, **75**, 1094; Amiel, Loeffler, and Ginsburg, *ibid.*, 1954, **76**, 3625; Bar-Shai and Ginsburg, preceding paper.

[2] Cope and Smith, *J. Amer. Chem. Soc.*, 1952, **74**, 5136.

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layer was extracted twice with ether. The combined ether solutions were distilled under reduced pressure. Light petroleum was added to the residue but crystallisation of the *alcohol* could be induced by scratching only after water (20 ml.) was added. The crystals were removed and washed until colourless with light petroleum, then having m. p. 41° (90 g.) (Found : C, 75·6; H, 10·0; O, 14·6. $C_{14}H_{26}O,1H_2O$ requires C, 75·6; H, 10·0; O, 14·4%). On drying, the substance is obtained as an oil. From the mother-liquor, *cyclo*octanone (19 g.) and 1-phenyl-*cyclo*octene (21 g.) were recovered by distillation.

1-*Phenyl*cyclo*octene Nitrosochloride.*—1-*Phenyl*cyclo*octene* was obtained in quantitative yield by dehydration of the above alcohol with concentrated phosphoric acid. It had b. p. 106°/5 mm., n_D^{20} 1·5610 (Found : C, 90·2; H, 9·95. $C_{14}H_{18}$ requires C, 90·3; H, 9·7%).

To 1-phenyl*cyclo*octene (21 g.) and *iso*pentyl nitrite (16 ml.) in glacial acetic acid (50 ml.) was added at 0° with stirring a mixture of concentrated hydrochloric acid (16 ml.) and acetic acid (10 ml.). The colourless crystalline *nitrosochloride* was filtered off, washed with cold ethanol and ether, and dried by suction; it had m. p. 95° (19 g.) (Found : N, 5·5; Cl, 14·0. $C_{14}H_{18}ONCl$ requires N, 5·6; Cl, 14·2%). 1-Phenyl*cyclo*octan-1-ol (22 g.) could be used equally well to yield the nitrosochloride (19 g.). The product is stable for months at 0°.

2-*Phenyl*cyclo*oct-2-enone Oxime.*—The nitrosochloride (10 g.) was added to a solution of potassium hydroxide (10 g.) in ethanol (50 ml.) and heated at 70° for 15—30 min. The resulting solution was poured into water (300 ml.) and after careful acidification with hydrochloric acid was steam-distilled. After removal of the ethanol and some 1-phenyl*cyclo*octene, the residue was cooled and filtered. The *oxime* forms colourless hexagonal plates, m. p. 150° (from ethanol), after sintering with loss of solvent of crystallisation at 140° (Found : C, 74·0; H, 8·9; N, 5·3. $C_{14}H_{17}ON,C_2H_5{\cdot}OH$ requires C, 73·5; H, 8·9; N, 5·4%).

2-*Phenyl*cyclo*oct-2-enone.*—(a) *From its oxime.* A solution of the oxime (1·8 g.) in ethyl methyl ketone (50 ml.) was added to a mixture of acetone (2 ml.), hydrochloric acid (1 : 1; 12 ml.), and cuprous oxide (2 g.) and the mixture was heated at 80° for 20 hr.[3] Water (100 ml.) was added, and the aqueous layer was extracted with ether. The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was dissolved in methyl*cyclo*hexane and washed with Claisen's alkali until the latter was colourless. The methyl*cyclo*hexane layer was washed with dilute acid and with water and dried (K_2CO_3). After removal of the solvent and distillation, the *ketone*, b. p. 110°/0·4 mm., was obtained (0·7 g.) and characterised as the 2 : 4-dinitrophenylhydrazone, m. p. 127° (from ethanol).

When the oxime was refluxed with aqueous oxalic acid, ω-benzoylheptanoic acid, m. p. 84—85° (from water), crystallised from the aqueous solution after steam-distillation of volatile material (Found : C, 71·6; H, 7·7. Calc. for $C_{14}H_{18}O_3$: C, 71·8; H, 7·7%). It gave no m. p. depression on admixture with the keto-acid obtained by oxidation of 1-phenyl*cyclo*octan-1-ol.[4]

(b) *From* 2-*phenyl*cyclo*octanone.* A mixture of 2-phenyl*cyclo*octanone (3 g.), *N*-bromosuccinimide (1·8 g.), and carbon tetrachloride (15 ml.) was refluxed for 90 min. After the usual working up, the residue was set aside at room temperature in collidine (20 ml.). Thence was recovered 2-phenyl*cyclo*oct-2-enone (2·8 g.), characterised as the 2 : 4-*dinitrophenylhydrazone*, yellow needles, m. p. 127° (from ethanol) (Found : C, 63·45; H, 5·3; N, 14·8. $C_{20}H_{20}O_4N_4$ requires C, 63·15; H, 5·3; N, 14·7%). Ultraviolet absorption (in MeOH) : $\lambda_{max.}$ 3620 Å (log ε 4·37). Infrared absorption (C=O) (in $CHCl_3$) : 1695 cm.$^{-1}$.

2-*Phenyl*cyclo*octanone.*—(a) 2-Phenyl*cyclo*oct-2-enone (1 g.) in ethanol (25 ml.) was hydrogenated in the presence of 5% palladised charcoal (0·5 g.) at atmospheric pressure. One mol. of hydrogen was absorbed during 30 min. Removal of the catalyst and solvent followed by distillation of the residue yielded the saturated *ketone*, b. p. 115°/0·4 mm., characterised as the yellow 2 : 4-*dinitrophenylhydrazone*, m. p. 146° (from ethanol) (Found : C, 62·8; H, 5·7; N, 14·3. $C_{20}H_{22}O_4N_4$ requires C, 62·8; H, 5·8; N, 14·65%), identical with that obtained by the epoxidation procedure (see below). Ultraviolet absorption (in MeOH) : $\lambda_{max.}$ 3510 Å (log ε 4·39).

(b) *Epoxidation procedure.*[3] Hydrogen peroxide (30%; 4·4 g.) was added at 40° to a mixture of 1-phenyl*cyclo*octene (5·5 g.), concentrated sulphuric acid (0·5 ml.), and glacial acetic acid (26 ml.). After being stirred at room temperature for 3 hr. the mixture was poured into hot water (60°; 200 ml.) and was stirred for 5 min., then neutralised with aqueous sodium hydroxide and extracted with ether. Evaporation of the ether followed by distillation yielded an oil, b. p. 100—116°/0·2 mm. This was added to ethanolic (20 ml.) potassium hydroxide

[3] Summerford and Dalton, *J. Amer. Chem. Soc.*, 1944, **66**, 1330.
[4] Fieser and Szmuszkovicz, *J. Amer. Chem. Soc.*, 1948, **70**, 3352.

(1·7 g.), and the mixture was refluxed for 1 hr. and poured into water (300 ml.). Ether-extraction followed by removal of the solvent and distillation gave two fractions, b. p. 80—96°/0·5 mm. and 100—120°/0·5 mm. The latter fraction showed absorption at 1685 cm.$^{-1}$ (C=O) and 1725 cm.$^{-1}$ (acetate C=O). Addition of 2 : 4-dinitrophenylhydrazine solution to this fraction yielded the 2 : 4-dinitrophenylhydrazone of 2-phenyl*cyclo*octanone, m. p. 146° (from ethanol) (1 g.).

When the Cope–Smith procedure [2] was followed in its entirety, 2-phenyl*cyclo*octanone was obtained and was characterised by the identical 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 146° (from ethanol), and as its semicarbazone, m. p. 154°. Cope and Smith [2] report m. p. 153·9—154·7° for the latter derivative.

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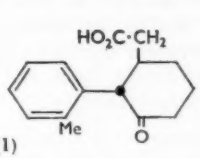
246. *Alicyclic Studies. Part VII.* An Alicyclic Approach to the Synthesis of Methylphenanthrenes and Benzo[c]phenanthrene.*

By YAIR KLIBANSKY and DAVID GINSBURG.

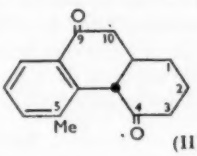
2-Aryl*cyclo*hex-2-enones are shown to be versatile intermediates for the synthesis of many substituted phenanthrenes.

THE efficacy of 2-aryl*cyclo*hex-2-enones as intermediates for construction of the phenanthrene system has been demonstrated through their use as acceptors in the Michael condensation.[1] Essentially the same approach was subsequently used to synthesise 2 : 9-dimethylphenanthrene by utilising the Grignard reaction of the carbonyl groups in the tricyclic diketone formed, as keys for introduction of methyl groups in their stead.[2] Further obvious uses of the carbonyl groups and differences in their reactivities for introduction of substituents in positions α to these key groups have been employed.[1]

In the present communication the same approach has been extended in that 2-*o*-tolyl-*cyclo*hex-2-enone has been prepared from 1-*o*-tolyl*cyclo*hexene and has been shown to undergo Michael condensation with benzyl malonate to give an adduct which upon debenzylation with hydrogen bromide in glacial acetic acid [3] and decarboxylation finally gives *trans*-3-oxo-2-*o*-tolyl*cyclo*hexylacetic acid (I). This acid was quantitatively cyclised by anhydrous hydrogen fluoride to 1 : 2 : 3 : 4 : 4*a* : 9 : 10 : 10*a*-octahydro-5-methyl-4 : 9-dioxophenanthrene (II). It has been shown that the 4-dioxolan can be formed selectively so that a methyl group can, for example, be introduced into the 10-position. This approach therefore affords a means for the synthesis of phenanthrenes substituted in any of the



(I)



(II)

positions 1, 2, 3, 4 (aromatic numbering) (depending upon the aryl group in the αβ-ethylenic ketone used as an acceptor in the Michael condensation), in the 5 or 10 position (aromatic numbering) by Grignard addition to the carbonyl groups followed by dehydration and dehydrogenation and in the 6 or 9 position α to the carbonyl functions as exemplified in the present work. In principle, many combinations of polyalkylphenanthrenes may be prepared by this versatile route.

* Part VI, preceding paper.

[1] Ginsburg and Pappo, *J.*, 1951, 938.
[2] Bergmann and Szmuszkovics, *J. Amer. Chem. Soc.*, 1953, **75**, 3226.
[3] Ben Ishai, *J. Org. Chem.*, 1954, **19**, 62.

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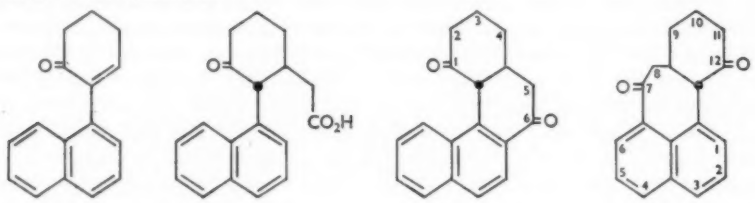
Analogously, derivatives of tetracyclic and higher polynuclear systems should be obtainable by a similar approach. For this reason the study of 2-α-naphthyl*cyclo*hex-2-enone as an acceptor in the Michael reaction was undertaken. As expected, this compound afforded a route to benzo[*c*]phenanthrene.

The oxime of 2-α-naphthyl*cyclo*hex-2-enone was prepared by dehydrochlorination of the nitrosochloride of 1-α-naphthyl*cyclo*hexene and afforded the αβ-ethylenic ketone (III) on acidic hydrolysis, whose structure was proved by dehydrogenation to the phenol and methylation to yield the known 2-α-naphthylanisole. Addition of benzyl sodiomalonate in boiling xylene to the unsaturated ketone, etc., led to *trans*-3-oxo-2-α-naphthyl*cyclo*hexylacetic acid (IV). Cyclisation of this acid with anhydrous hydrogen fluoride afforded the octahydrodioxobenzophenanthrene (V). Alternatively, if the cyclisation was carried out with polyphosphoric acid, a reagent often used for formation of cyclic seven-membered ketones, an isomeric ketone (VI) was obtained and characterised as its 2 : 4-dinitrophenylhydrazone. Huang-Minlon reduction of the keto-acid (IV) gave *trans*-2-α-naphthyl*cyclo*hexylacetic acid which on cyclisation with hydrogen fluoride yielded the octahydro-6-oxobenzophenanthrene. The diketone (V) was reduced to the hydrocarbon, 1 : 2 : 3 : 4 : 4*a* : 5 : 6 : 12*c*-octahydrobenzo[*c*]phenanthrene (numbering: Ring Index 2807) by treatment of its tetrabenzyl bisdithioacetal with Raney nickel. Dehydrogenation of the hydrocarbon with palladised carbon yielded the known benzo[*c*]phenanthrene.

When the diketone (V) was treated with ethylene glycol in the presence of toluene-*p*-sulphonic acid the 1-oxo-group was selectively converted into the ketal, so that in this case also it is possible to introduce alkyl groups selectively into the skeleton. A by-product obtained during the reaction had the empirical formula $C_{36}H_{24}$ and showed no carbonyl or hydroxyl absorption in the infrared spectrum; presumably it is formed by self-condensation of the diketone with concomitant or subsequent cyclodehydration; its structure was not elucidated.



(III) (IV) (V) (VI)

The infrared absorption of the tetracyclic diketone (V) is worthy of note. In contradistinction to 1 : 2 : 3 : 4 : 4*a* : 9 : 10 : 10*a*-octahydro-4 : 9-dioxophenanthrene which exhibits a saturated carbonyl band at 1710 cm.$^{-1}$ and an acetophenone-type carbonyl band at 1695 cm.$^{-1}$, diketone (V) has one broad absorption band at 1702 cm.$^{-1}$, intermediate between the two. The infrared data for the significant functional groups in the various products now obtained are reported in the Experimental section.

Experimental

1-o-*Tolyl*cyclo*hexene*.—*o*-Tolylmagnesium bromide was prepared from *o*-bromotoluene (172 g.) and magnesium (24 g.) in dry ether (1 l.). *cyclo*Hexanone (98 g.) in ether (100 ml.) was added to the Grignard solution at −10° to −5°. Then the mixture was refluxed for 3 hr., cooled, and decomposed with saturated ammonium chloride solution. After the usual working up, the solvent and unchanged starting materials were removed at the water-pump. The yellow-brown residual oil was boiled with anhydrous oxalic acid (20 g.) and toluene (400 ml.) until no more water was obtained in the azeotropic collector (90 min.). After the usual working up, the *cyclo*alkene was obtained as a colourless oil, b. p. 108—111°/1 mm. (110 g., 64%).

2-o-*Tolyl*cyclo*hex-2-enone*.—Cold *n*-pentyl nitrite (88 g., 0·75 mole) was added with stirring at 8° to a mixture of 1-*o*-tolyl*cyclo*hexene (100 g., 0·58 mole) and propionic acid (200 ml.). Concentrated hydrochloric acid (75 ml.) was then added dropwise at −15° to −12° with stirring,

and the mixture was stirred for a further 3 hr. at −12°. The temperature was raised to 0° and the mixture was poured into a cold solution of ethanolic (2 l.) potassium hydroxide (560 g.) and the solution was refluxed for 30 min., then steam-distilled until 5 l. of distillate were obtained (colourless crystals appear in the condenser). The residue was cooled, diluted (stirring) with water and ice, and neutralised with cold hydrochloric acid. A brown flocculent precipitate of the oxime was obtained, filtered off, washed with water, and dried (70 g., 60%).

The crude oxime (24 g.) was refluxed with dilute sulphuric acid (50 ml. of concentrated acid + 300 ml. of water) for 3 hr. After cooling, extraction with ether–benzene, washing of the extract with saturated aqueous sodium hydrogen carbonate and with water, and drying (Na_2SO_4), the solvents were removed and the residue was distilled in a high vacuum. The αβ-ethylenic ketone was obtained as a light yellow oil, b. p. 152—154°/2 mm. (12 g., 54%). Ultraviolet absorption: $\lambda_{max.}$ 2550 Å (log ε 3·98 in EtOH). Infrared absorption (in $CHCl_3$): 1675 cm.$^{-1}$ (C=C·C=O).

The ketone formed the 2 : 4-*dinitrophenylhydrazone* as orange-red plates, m. p. 128° (from ethanol–ethyl acetate) (Found: C, 62·3; H, 5·1; N, 15·7. $C_{19}H_{18}O_4N_4$ requires C, 62·3; H, 5·0; N, 15·3%). Ultraviolet absorption: $\lambda_{max.}$ 3810—3860 Å (log ε 4·48 in $CHCl_3$). The *oxime*, obtained by the pyridine method, formed elongated rhombs, m. p. 152·5—153° (from aqueous ethanol) (Found: C, 77·6; H, 7·8; N, 7·2. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·5; N, 7·0%).

trans-3-*Oxo*-2-*o*-*tolyl*cyclo*hexylacetic Acid* (I).—A mixture of 2-*o*-tolyl*cyclo*hex-2-enone (18 g., 0·1 mole), freshly distilled benzyl malonate (36 g., 0·13 mole), and potassium *tert.*-butoxide [from 420 mg. of potassium and 6·6 ml. of *tert.*-butyl alcohol (0·013 mole)] was set aside for 15 hr. at 60°, then cooled, acidified with acetic acid, diluted with ether, and washed with water to remove precipitated potassium acetate. The ethereal solution was dried (Na_2SO_4) and the solvent was removed. To the residue was added a saturated glacial acetic solution of hydrogen bromide (100 g.; *ca.* 25% HBr). The mixture was kept overnight at room temperature, then refluxed for 4 hr., and the acetic acid and part of the benzyl bromide formed were removed at reduced pressure. This treatment was repeated with an additional portion (100 g.) of hydrogen bromide in acetic acid. After the acetic acid and benzyl bromide had again been removed the residue was diluted with ether and the malonic acid was extracted several times by saturated sodium carbonate solution and then once with 5% sodium hydroxide solution. The combined alkaline extracts were washed once with ether and then acidified, while cooling, with hydrochloric acid. Unchanged αβ-ethylenic ketone can be recovered from the organic phase. The oily malonic acid precipitated in the aqueous phase was taken up in ether and on removal of the ether the residual oil was heated at 200° until evolution of carbon dioxide was complete. The residual viscous monobasic *acid* crystallised (14 g.). It had b. p. 122°/0·4 mm., m. p. 101—103° (from heptane) (Found: C, 72·9; H, 7·0. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). Infrared absorption (in $CHCl_3$): 3300—2900 (OH of CO_2H), 3500 (OH), 1710 cm.$^{-1}$ (v.s.; includes carbonyl C=O and carboxyl C=O).

The *methyl ester*, prepared by diazomethane, slowly crystallised as plates, m. p. 77—78° (from ethanol) (Found: C, 73·7; H, 7·4. $C_{16}H_{20}O_3$ requires C, 73·9; H, 7·7%). Its 2 : 4-*dinitrophenylhydrazone* formed golden crystals, m. p. 153—154° (from ethanol–ethyl acetate) (Found: C, 60·0; H, 5·2; N, 12·4. $C_{22}H_{24}O_6N_4$ requires C, 60·0; H, 5·5; N, 12·7%).

1 : 2 : 3 : 4 : 4a : 9 : 10 : 10a-*Octahydro*-5-*methyl*-4 : 9-*dioxophenanthrene* (II).—The above acid (I) (2·5 g.) was treated with anhydrous hydrogen fluoride (*ca.* 50 g.) and after 4 hr. the mixture was worked up in the usual way. The *diketone* (2 g.) gave light yellow crystals, m. p. 128—130°, from aqueous ethanol (Found: C, 78·8; H, 7·3. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·0%). Infrared absorption (in $CHCl_3$): 1683 (C=O adjacent to aromatic nucleus), 1713 cm.$^{-1}$ (C=O in six-membered ring). Ultraviolet absorption: $\lambda_{max.}$ 2550, 3000 Å (log ε 4·04, 3·28 in EtOH). The *mono-oxime* formed colourless crystals, m. p. 245—247°, from ethanol [Found: C, 73·3; H, 7·0. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·0. Calc. for $C_{15}H_{18}O_2N_2$ (dioxime): C, 69·8; H, 7·0%]. The orange-red *mono*-2 : 4-*dinitrophenylhydrazone* had m. p. 219·5—221·5° (from ethanol–ethyl acetate) (Found: C, 61·3; H, 5·5; N, 13·9. $C_{21}H_{20}O_5N_4$ requires C, 61·8; H, 4·9; N, 13·7%). Ultraviolet absorption: $\lambda_{max.}$ 3850 Å (log ε 4·62 in $CHCl_3$). Infrared absorption (in $CHCl_3$): 1718 cm.$^{-1}$. The 4-oxo-group is therefore free in these derivatives.

4-*Ethylenedioxy*-1 : 2 : 3 : 4 : 4a : 9 : 10 : 10a-*octahydro*-5-*methyl*-9-*oxophenanthrene*.—The diketone (4·5 g.) was heated with benzene (20 ml.), ethylene glycol (10 ml.), and toluene-*p*-sulphonic acid (150 mg.) for 3 hr. in a flask attached to an azeotropic collector. After cooling

and neutralisation of the acid catalyst with a small quantity of sodium methoxide, water was added and the benzene layer dried (Na_2SO_4). The benzene was removed and the residual *dioxolan* (4·2 g., 77%) gave colourless crystals, m. p. 72—73°, from hexane (Found : C, 74·5; H, 7·4. $C_{17}H_{20}O_3$ requires C, 75·0; H, 7·4%). Infrared absorption (in $CHCl_3$) : 1688 cm.$^{-1}$ (C=O adjacent to aromatic ring), 1157, 1083 cm.$^{-1}$ (ketal).

1 : 2 : 3 : 4 : 4a : 9 : 10 : 10a-*Octahydro*-5 : 10-*dimethyl*-4 : 9-*dioxophenanthrene*.—A solution of the dioxolan (5·5 g., 0·02 mole) in dry ether–benzene (3 : 1; 20 ml.) was added dropwise with stirring to a boiling suspension of sodium hydride (0·6 g., 0·025 mole) in dry ether. After refluxing for 5 hr. (it may be necessary to clean the surface of the sodium hydride by the careful addition of a drop of ethanol) the mixture was cooled and methyl iodide (5·1 g., 0·035 mole) in dry benzene (5 ml.) was added. The mixture was kept overnight at room temperature and finally refluxed for 3 hr. After the usual working up, the ethylenedioxy-derivative of the dimethyl derivative was obtained as a yellow oil which afforded light yellow needles (5·1 g.). Infrared absorption of the crude dioxolan in $CHCl_3$ showed the presence of the free C=O group at 1683 cm.$^{-1}$ and the ketal at 1150, 1080 cm.$^{-1}$. A strong band was found at 1379 cm.$^{-1}$ (*C*-Me) in much higher concentration than in the starting material.

The crude ketal (1 g.) was warmed with ethanol (25 ml.), water (5 ml.), and concentrated hydrochloric acid (0·5 ml.) on the steam-bath for 2 hr. The usual working up gave the 5 : 10-*dimethyl derivative* (0·82 g.), m. p. 140—142° (from heptane) (Found : C, 79·3; H, 7·2. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·4%). Infrared absorption (in $CHCl_3$) : 1713 (*cyclo*hexanone C=O), 1683 cm.$^{-1}$ (acetophenone C=O). Ultraviolet absorption : $\lambda_{max.}$ 2550, 2970 Å (log ε 4·07, 3·34 in EtOH).

The dark red *mono*-2 : 4-*dinitrophenylhydrazone* had m. p. 223—225° (from ethanol–ethyl acetate) (Found : C, 61·9; H, 5·1; N, 13·6. $C_{22}H_{22}O_5N_4$ requires C, 62·6; H, 5·2; N, 13·2%). Infrared absorption (in $CHCl_3$) : 1719 cm.$^{-1}$ (free *cyclo*hexanone C=O). Ultraviolet absorption : $\lambda_{max.}$ 3850 Å (log ε 4·67 in $CHCl_3$). The *dioxime*, formed in hot pyridine by a large excess of hydroxylamine (4 hr.), was yellowish needles, m. p. 254—255° (decomp.) (from aqueous ethanol) (Found : C, 70·5; H, 7·3; N, 9·7. $C_{16}H_{20}O_2N_2$ requires C, 70·6; H, 7·4; N, 10·3%).

1-α-*Naphthyl*cyclo*hexene*.—In the preparation of the Grignard reagent on a molar scale the method described in *Org. Synth.* was followed.[4] *cyclo*Hexanone (100 g.) in dry ether (400 ml.) was added during 30 min. with vigorous stirring at −15°. Stirring was continued for 15 min. at this temperature and the mixture was then refluxed with stirring for 3 hr. After the usual working up and removal of unchanged starting materials a crude alcohol was obtained (255 g.). This was dehydrated in the usual way [5] with oxalic acid in boiling toluene. Water (16 ml.) was obtained during 1 hr. The *cyclo*alkene distilled at 136—140°/0·5 mm. (160 g., 70%), crystallised, and formed colourless needles (from methanol), m. p. 47—48° (Cook *et al.*[6] give m. p. 46°). The *picrate*, prepared in ethanol, gave yellow-orange crystals, m. p. 124—125° (Cook *et al.* give m. p. 124·5—125·5°).

2-α-*Naphthyl*cyclo*hex*-2-*enone* (III).—The preparation was analogous to that described for 2-*o*-tolyl*cyclo*hex-2-enone (above). From the *cyclo*alkene (60 g.), the analogous mixture containing the nitrosochloride was poured into ethanolic (1·5 l.) potassium hydroxide (300 g.) and refluxed for 30 min. Steam-distillation was then carried out until 2·9 l. of distillate had been obtained. After treatment analogous to that described above, brown crystalline oxime (66 g., 95%) was obtained.

The oxime (55 g.) was hydrolysed by heating it in dioxan (300 ml.) with 40% aqueous formaldehyde (300 ml.) and concentrated hydrochloric acid (60 ml.) on the steam-bath for 15 min. The mixture was cooled and diluted with water. A brown flaky precipitate was obtained. The mixture was extracted several times with ether–benzene, and the organic phase was filtered to remove insoluble material (4·5 g., 8%) whose infrared spectrum indicated that it may be a lactam (formed by Beckmann rearrangement of the oxime); it was not investigated further. The organic phase was then dried (Na_2SO_4) and the solvents were removed. The viscous oily residue was distilled and the αβ-ethylenic *ketone* was obtained as a yellow oil, b. p. 135—150°/0·5 mm. (37 g., 75%), colourless needles, m. p. 101·5—103° (from heptane) (Found : C, 86·7; H, 6·4. $C_{16}H_{14}O$ requires C, 86·5; H, 6·4%). Infrared absorption (in $CHCl_3$) : 1670 cm.$^{-1}$ (C=C–C=O). Ultraviolet absorption : $\lambda_{max.}$ 3850 Å (log ε 4·39 in $CHCl_3$). The

[4] *Org. Synth.*, Wiley, New York, 1943, Coll. Vol. II, p. 425.
[5] Ginsburg and Pappo, *J.*, 1951, 516.
[6] Cook, Hewett, and Lawrence, *J.*, 1936, 71.

2 : 4-*dinitrophenylhydrazone* formed red needles, m. p. 168—169° (from ethanol–ethyl acetate) (Found : C, 65·2; H, 4·9; N, 13·5. $C_{22}H_{18}O_4N_4$ requires C, 65·7; H, 4·5; N, 13·9%). Ultraviolet absorption : $\lambda_{max.}$ 3860 Å (log ε 4·40 in $CHCl_3$). The *oxime*, formed by the pyridine method, gave nearly colourless needles with a greyish cast, m. p. 211—212° (from ethanol) (Found : C, 81·1; H, 6·8. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·4%).

Dehydrogenation of 2-α-*Naphthyl*cyclo*hex-2-enone* : 2-α-*Naphthylanisole*.—A mixture of the ketone (1·5 g.), 30% palladised charcoal (0·75 g.), and *p*-cymene (20 ml.) was refluxed for 5 hr. under nitrogen. After cooling and dilution with ether the catalyst was removed and washed with ether. The filtrate was extracted several times with Claisen's alkali. The alkaline extract was slowly acidified in the cold with concentrated hydrochloric acid, and the phenol was taken up in ether. After drying (Na_2SO_4) the ether was removed on the steam-bath and traces of *p*-cymene were removed under reduced pressure. The residue was dissolved in a small excess of 10% aqueous sodium hydroxide and approximately the equivalent quantity of dimethyl sulphate was added. The mixture was heated on the steam-bath for 15 min. and after the usual working up, light tan crystals of 2-α-naphthylanisole were obtained, having m. p. 90—91·5° (from light petroleum). Orchin [7] reports m. p. 91·2—92·6° (Found : C, 87·4; H, 6·2. Calc. for $C_{17}H_{14}O$: C, 87·2; H, 6·0%). Infrared absorption (in $CHCl_3$) : 1070—1000, 1300—1170 cm.$^{-1}$ (OMe).

trans-2-α-*Naphthyl*-3-*oxo*cyclo*hexylacetic Acid* (IV).—To a well-stirred mixture, under nitrogen, of sodium hydride (5·76 g., 0·24 mole) and dry xylene (85 ml.) was added in portions a solution of benzyl malonate (72 g., 0·25 mole) in dry xylene (210 ml.). The mixture was refluxed until the sodium hydride had reacted (2—3 hr.), then cooled to room temperature. A solution of 2-α-naphthyl*cyclo*hex-2-enone (35 g., 0·16 mole) in a minimum of dry xylene was added in one portion and the mixture was refluxed for 5 hr. After cooling and acidification with acetic acid the working up was analogous to that described for the preparation of 3-oxo-2-*o*-tolyl*cyclo*hexylacetic acid (see above). As described above, unchanged ketone can be recovered.

Decarboxylation of the crude malonic acid was effected at 200°. The oily residue was distilled and the *keto-acid* had b. p. 134°/3 mm. (15 g., 33%), m. p. 119—120° (needles from heptane) (Found : C, 76·5; H, 6·6. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%). Infrared absorption (in $CHCl_3$) : very broad strong band at 1715 cm.$^{-1}$ (C=O of ketone and of carboxyl). The methyl ester (diazomethane) had b. p. 83°/0·5 mm., n_D^{25} 1·50184; it gave a very strong infrared band at 1729 cm.$^{-1}$, intermediate between the values to be expected for a saturated ketonic group and a saturated ester group.

trans-2-α-*Naphthyl*cyclo*hexylacetic Acid*.—The keto-acid (3·5 g.) was reduced by the Huang-Minlon procedure employing potassium hydroxide (2·4 g.), hydrazine hydrate (1·5 ml.), and diethylene glycol (18 ml.). Heating for 4 hr. at 200° was insufficient for complete reduction. The reduced *acid* (0·6 g.) was obtained by distillation (b. p. 165—180°/1·4 mm.) as a viscous yellow oil which slowly crystallised and formed colourless needles, m. p. 84—86°, from heptane (Found : C, 79·9; H, 6·9. $C_{18}H_{20}O_2$ requires C, 80·6; H, 7·5%).

1 : 2 : 3 : 4 : 4a : 5 : 6 : 12c-*Octahydro*-1 : 6-*dioxobenzo*[c]*phenanthrene* (V).—The keto-acid (2·3 g.) was treated with anhydrous hydrogen fluoride (*ca.* 50 g.). After the usual working up the crude diketone was obtained as a brownish oil (2·1 g., 95%) with a characteristic odour. A benzene solution of the oil was filtered through a column of neutral alumina. Evaporation of the eluate afforded a light yellow oil which soon crystallised to needles of the *diketone*. It formed yellowish needles, m. p. 40—41° (from heptane), and occasionally crystallised as glistening yellowish plates of the same m. p. which did not depress the m. p. of the needles (Found : C, 81·5; H, 6·2. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·0%). The infrared spectrum showed a very strong band at 1702 cm.$^{-1}$ intermediate between a *cyclo*hexanone- and an acetophenone-type ketone, and bands at 1278 (acetophenone) and 1176 cm.$^{-1}$ (*cyclo*hexanone). The *bis*-2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 258—260° (decomp.), from methanol–ethyl acetate (Found : C, 57·7; H, 3·9; N, 17·7. $C_{30}H_{24}O_8N_8$ requires C, 57·7; H, 3·8; N, 17·9%). Ultraviolet absorption : $\lambda_{max.}$ 3920 Å (log ε 4·77 in $CHCl_3$). The *dioxime*, prepared in pyridine, formed needles, m. p. 117—119°, from aqueous methanol (Found : C, 73·4; H, 5·7; N, 9·1. $C_{18}H_{18}O_2N_2$ requires C, 73·5; H, 6·2; N, 9·5%).

1 : 2 : 3 : 4 : 4a : 5 : 6 : 12c-*Octahydro*-6-*oxobenzo*[c]*phenanthrene*.—2-α-Naphthyl*cyclo*hexylacetic acid (1·0 g.) was treated with anhydrous hydrogen fluoride (*ca.* 30 g.). The crude ketone

[7] Orchin, *J. Amer. Chem. Soc.*, 1948, **70**, 495.

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(0·9 g., 92%) was purified by filtration of its benzene solution through neutral alumina, and the eluate upon evaporation gave the ketone as a yellow oil (0·83 g.) which partially crystallised in the refrigerator. Infrared absorption (in $CHCl_3$) : 1709 cm.$^{-1}$, possibly indicating diminished coplanarity with the aromatic ring. It was characterised as the 2 : 4-*dinitrophenylhydrazone* which formed dark red plates, m. p. 186—188° (from ethanol) (Found : C, 66·5; H, 5·4; N, 13·5. $C_{24}H_{22}O_4N_4$ requires C, 67·0; H, 5·1; N, 13·0%) [ultraviolet absorption $\lambda_{max.}$ 3930 Å (log ε 4·55 in $CHCl_3$)], and as *oxime*, prepared in pyridine, needles, m. p. 118—123° (from aqueous ethanol) (Found : N, 5·7. $C_{18}H_{19}ON$ requires N, 5·3%).

Reductions of the Diketone Bisdithioacetals with Raney Nickel.—(*a*) The diketone (V) (1 g.) was treated in dioxan (5 ml.) with ethanethiol (2 g., 8 equivs.) and boron trifluoride–ether complex (1·5 ml.). A strong exothermic reaction occurred and crystals appeared in the solution. After 36 hr. at room temperature aqueous sodium hydrogen carbonate was added, whereupon the crystals dissolved. The organic phase was separated, the aqueous layer was extracted with ether, the organic phases were combined, washed with water, and dried (Na_2SO_4), and the ether and excess of thiol were removed on the steam-bath. The residue was refluxed in ethanol (100 ml.) with Raney nickel (15 g.) for 6 hr. After removal of the nickel and ethanol a brown oil, presumably the 1-ketone was characterised as the orange 2 : 4-*dinitrophenylhydrazone*, m. p. 214—216° (from ethanol) (Found : C, 66·6; H, 5·3. $C_{24}H_{22}O_4N_4$ requires C, 67·0; H, 5·1%).

(*b*) The 1 : 6-diketone (1 g.) was treated in dry dioxan (5 ml.) with toluene-ω-thiol (2 g., 4 equivs.) and boron trifluoride–ether complex (1 ml.). A strong exothermic reaction set in and a heavy crystalline deposit was formed. Working up was similar to that described in (*a*) but the residue was refluxed in dry dioxan (130 ml.) with active Raney nickel [8] (10 g.) for 5 hr. After removal of the catalyst and solvent, the viscous residue was distilled (b. p. 126—128°/0·2 mm.) and crystallised slowly at room temperature, affording colourless prisms and platelets. These were removed and the small amount of adhering oil was washed away with cold methanol. The crystals, m. p. 48—50°, appeared to be the tri- or tetra-benzyl bisdithioacetal (Found : C, 77·4; H, 6·5; S, 16·0. Calc. for $C_{19}H_{38}OS_2$: C, 75·7; H, 6·1; S, 15·5. Calc. for $C_{46}H_{44}S_4$: C, 76·2; H, 6·1; S, 17·7%).

The residue from the distillation was purified by filtering its solution in benzene–light petroleum through neutral alumina, followed by elution with light petroleum. The hydrocarbon was obtained as needles, m. p. 47°. Its infrared spectrum showed no oxygen functions but only the bands at 1604 and 1492 (aromatic C=C), 2910 and 1454 (CH_2), and 3040 cm.$^{-1}$ (aromatic CH).

Benzo[c]*phenanthrene.*—The hydrocarbon just described (100 mg.) was heated with 30% palladised carbon (15 mg.) at 310—320° under nitrogen for 1 hr. After cooling and extraction with hot benzene, the catalyst was removed. Concentration of the benzene solution afforded colourless needles of benzo[*c*]phenanthrene, m. p. and mixed m. p. 69° (from ethanol) (lit., m. p. 68°,[9] 67·5—68·3° [10]) (Found : C, 94·7; H, 5·3. Calc. for $C_{18}H_{12}$: C, 94·7; H, 5·3%). The picrate was prepared in ethanol on the steam-bath, and crystallised as red needles, m. p. 125—126° (lit., m. p. 126—127°,[9] 128—128·5° [10]).

1-*Ethylenedioxy*-1 : 2 : 3 : 4 : 4a : 5 : 6 : 12c-*octahydro*-6-*oxobenzo*[c]*phenanthrene.*—The diketone (V) (1·5 g.), toluene (10 ml.), ethylene glycol (3 ml.), and toluene-*p*-sulphonic acid (45 mg.) were refluxed for 8 hr. under an azeotropic separator, giving the *dioxalan* as yellowish needles, m. p. 136—138° (from toluene) (Found : C, 77·9; H, 6·0. $C_{20}H_{20}O_3$ requires C, 77·9; H, 6·5%). Infrared absorption (in $CHCl_3$) : 1678 (acetophenone C=O), 1183, 1156, 1096 cm.$^{-1}$ (ketal).

A *by-product* was obtained in the reaction flask during the boiling period. It formed glistening yellow plates, m. p. *ca.* 340° with some pre-sintering (Found : C, 94·7; H, 5·2. $C_{36}H_{24}$ requires C, 94·7; H, 5·3%). It was not investigated further.

Cyclisation of 2-α-*Naphthyl*-3-*oxo*cyclo*hexylacetic Acid by Polyphosphoric Acid.*—The acid (2 g.) was warmed on the steam-bath with polyphosphoric acid (60 g.) for 4 hr. with occasional shaking. After cooling and dilution with water, the turbid solution was extracted several times with ether. The ether extract was washed with aqueous sodium carbonate and with water and dried (Na_2SO_4). After removal of the ether an oily residue (1·2 g.) was obtained. The starting

[8] *Org. Synth.*, Wiley, New York, 1955, Coll. Vol. III, p. 181.
[9] Cook, *J.*, 1931, 2524.
[10] Bachmann and Edgerton, *J. Amer. Chem. Soc.*, 1940, **62**, 2970.

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material (0·3 g.) was recovered by acidification of the sodium carbonate extract. The infrared spectrum showed strong bands at 1712 and 1678 cm.$^{-1}$. No hydroxyl absorption was observed. Benzosuberone has a band at 1678 cm.$^{-1}$ (C=O).

The crude product was treated with 2 : 4-dinitrophenylhydrazine solution and the mixture of hydrazones thus obtained was dissolved in benzene and chromatographed on neutral alumina. The major fraction formed red rods and rhombs, m. p. 283° (decomp.) (from ethanol–ethyl acetate) (Found : C, 57·4; H, 3·8; N, 17·5. $C_{30}H_{24}O_8N_8$ requires C, 57·7; H, 3·8; N, 17·9%). This is formulated as the 2 : 4-*dinitrophenylhydrazone* of 7 : 8 : 8*a* : 9 : 10 : 11 : 12 : 12*a*-octahydro-7 : 12-dioxobenzo[4 : 5]*cyclo*hepta[1 : 2 : 3-*de*]naphthalene (VI). Ultraviolet absorption : $\lambda_{max.}$ 3910 Å (flat) (log ε 4·74 in $CHCl_3$). Two other bands were observed on the column but elution gave negligible material. The corresponding derivative of (V) was not obtained.

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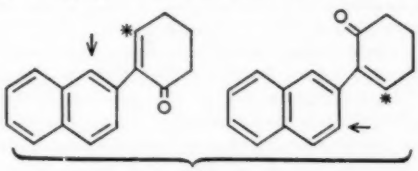
247. *Alicyclic Studies. Part VIII.* An Alicyclic Approach to the Synthesis of Chrysene.*

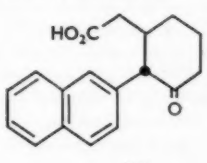
By YAIR KLIBANSKY and DAVID GINSBURG.

2-β-Naphthyl*cyclo*hex-2-enone was prepared *via* the nitrosochloride of 1-β-naphthyl*cyclo*hexene. Michael condensation of this ketone with benzyl malonate affords an adduct which on debenzylation and decarboxylation affords *trans*-2-β-naphthyl-3-oxo*cyclo*hexylacetic acid. Hydrogen fluoride cyclises this keto-acid to 1 : 2 : 3 : 4 : 4*a* : 11 : 12 : 12*a*-octahydro-4 : 11-dioxochrysene. Reduction of the diketone by sodium borohydride, followed by dehydration and dehydrogenation, yields chrysene.

IN the preceding paper it was shown that 2-α-naphthyl*cyclo*hex-2-enone acts as an acceptor in the Michael condensation, and its adduct with benzyl malonate is an intermediate in the synthesis of benzo[*c*]phenanthrene. In that case the result confirmed expectation but for the similar adduct of 2-β-naphthyl*cyclo*hex-2-enone (I) it is difficult to prophesy the direction of cyclisation of the keto-acid (II). From structures (I) it may be seen that an acetic acid side chain in the starred position can, in principle, be cyclised to either of the positions marked with an arrow. Perhaps a mixture of two products might be formed. It is known, for example, that γ-2-phenanthrylbutyric acid is cyclised in 23% yield to a benz[*a*]anthracene precursor by means of hydrogen fluoride [1] but cyclisation of the corresponding acid chloride with stannic chloride gives the isomeric hydrochrysene in excellent yield.[2] It is clear from the work of other authors who used 85% sulphuric acid as the cyclising agent that mixtures of both ketones must be formed.[3]



(I)



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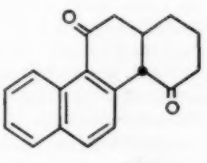

(III)

trans-2-β-Naphthyl-3-oxo*cyclo*hexylacetic acid (II) was prepared by debenzylation and decarboxylation of the adduct of the αβ-ethylenic ketone (I) with benzyl malonate. Cyclisation with hydrogen fluoride afforded 1 : 2 : 3 : 4 : 4*a* : 11 : 12 : 12*a*-octahydro-4 : 11-dioxochrysene (III). The crude ketone was reduced with sodium borohydride to the diol

* Part VII, preceding paper.

[1] Fieser and Johnson, *J. Amer. Chem. Soc.*, 1939, **61**, 1647.
[2] Bachmann and Struve, *J. Org. Chem.*, 1939, **4**, 456.
[3] Haworth and Mavin, *J.*, 1933, 1012; Burger and Mosettig, *J. Amer. Chem. Soc.*, 1937, **59**, 1302.

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which, without isolation, was dehydrated and dehydrogenated with palladised charcoal to yield chrysene. Since similar dehydrogenation of various hydrobenz[*a*]anthracenes yields the corresponding benz[*a*]anthracenes [2,4] without rearrangement to the chrysene ring system and none of the easily isolable benz[*a*]anthracene was obtained in the present work, it is believed that in this case cyclisation gives exclusively the chrysene precursor.

Here, also, as in the case of 1 : 2 : 3 : 4 : 4*a* : 5 : 6 : 12*c*-octahydro-1 : 6-dioxobenzo[*c*]-phenanthrene,[5] the diketone (III) exhibited a broad carbonyl infrared absorption band at 1702 cm.$^{-1}$, intermediate between the value expected for the saturated carbonyl group and that for the one adjacent to the aromatic nucleus.

Analogous Michael condensations of 2-β-naphthyl*cyclo*pent-2-enone and 2-β-naphthyl-*cyclo*hept-2-enone [6] with the view of obtaining tetracyclic systems are in progress.

Experimental

1-β-*Naphthyl*cyclo*hexene*.—To a solution of β-naphthyl-lithium [7] prepared from β-bromonaphthalene (10 g.) was added at −10° with vigorous stirring, under nitrogen, a solution of *cyclo*hexanone (4·5 g.) in dry ether (8 ml.). A white precipitate was formed. The temperature was raised to 25° during 2·5 hr. and the mixture left overnight. After the usual working up the *cyclo*alkene was distilled (b. p. 150—156°/0·7 mm.; 7·5 g., 75%); it formed colourless needles, m. p. 59°, from methanol (lit.,[8] m. p. 61—62°) (Found: C, 92·7; H, 7·7. Calc. for $C_{16}H_{16}$: C, 92·3; H, 7·7%). The picrate formed red needles, m. p. 78° (lit.,[8] m. p. 78°).

A higher-boiling fraction (1 g.) obtained in the distillation (b. p. >175°/0·7 mm.) gave a grey solid which formed yellowish plates, m. p. 187—188°, from benzene. This was ββ′-dinaphthyl (Found: C, 94·6; H, 5·7. Calc. for $C_{20}H_{14}$: C, 94·5; H, 5·5%).

2-β-*Naphthyl*cyclo*hex-2-enone*.—This preparation was carried out as was that of its α-naphthyl isomer.[5] From 10 g. of the *cyclo*hexene, 10·5 g. of crude oxime (91%) were obtained. The αβ-ethylenic *ketone* was obtained from the oxime in 65% yield. It had b. p. 160—175°/0·5 mm. and was purified by filtering its benzene solution through neutral alumina. The residual oil after evaporation of the benzene formed colourless needles, m. p. 96° (from heptane) (Found: C, 86·1; H, 6·0. $C_{16}H_{14}O$ requires C, 86·5; H, 6·3%). Infrared absorption (in $CHCl_3$): 1674 cm.$^{-1}$ (C=C−C=O). The 2 : 4-*dinitrophenylhydrazone* was obtained as short orange needles or leaves, m. p. 209·5—211° (from ethanol–ethyl acetate) (Found: C, 65·3; H, 4·5; N, 13·5. $C_{22}H_{18}O_4N_4$ requires C, 65·7; H, 4·5; N, 13·9%). Ultraviolet absorption: $\lambda_{max.}$ 3870 Å (log ε 4·37 in $CHCl_3$). The *oxime* formed colourless needles, m. p. 205°, from aqueous ethanol (Found: C, 80·8; H, 6·0; N, 5·5. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·3; N, 5·9%).

trans-2-β-*Naphthyl*-3-*oxo*cyclo*hexylacetic Acid*.—This *acid*, prepared in 33% yield as was its α-naphthyl isomer,[5] crystallised as needles, m. p. 181—182°, from heptane (Found: C, 76·1; H, 6·1. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%). The infrared spectrum showed a very strong broad band at 1710 cm.$^{-1}$, both carbonyl functions overlapping. Most (55%) of the original ketone can be recovered after debenzylation and alkali-extraction.

1 : 2 : 3 : 4 : 4a : 11 : 12 : 12a-*Octahydro*-4 : 11-*dioxochrysene*.—The keto-acid (4 g.) yielded the diketone (3·2 g., 86%) by cyclisation with hydrogen fluoride. The procedure paralleled that for the cyclisation of the α-naphthyl isomer.[5] The *diketone* formed yellowish needles, m. p. 35—40°, from pentane. The infrared spectrum showed a very broad band at 1702 cm.$^{-1}$ and bands at 1278 (acetophenone C=O) and 1176 cm.$^{-1}$ (*cyclo*hexanone C=O). The *bis*-2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 261—262·5° (decomp.), from ethanol–ethyl acetate. It sometimes crystallised as orange-red needles of the same m. p. and ultraviolet absorption (Found: C, 57·7; H, 3·75; N, 17·8. $C_{30}H_{24}O_8N_8$ requires C, 57·7; H, 3·8; N, 17·9%). Ultraviolet absorption: $\lambda_{max.}$ 3140, 3910 Å (log ε 4·13, 4·87 in $CHCl_3$). The *dioxime*, prepared in pyridine, formed colourless needles, m. p. 145—145·5°, from water (Found: C, 73·4; H, 6·0. $C_{18}H_{18}O_2N_2$ requires C, 73·5; H, 6·1%).

Chrysene.—(*a*) The diketone (1·5 g.) was dissolved in methanol (50 ml.) and sodium borohydride (1·8 g.) was added in small portions with shaking. The solution began nearly to boil.

[4] Bachmann and Chemerda, *J. Org. Chem.*, 1941, **6**, 36, 50.
[5] Klibansky and Ginsburg, preceding paper.
[6] Bar-Shai and Ginsburg, *J.*, 1957, 1289.
[7] Gilman and Moore, *J. Amer. Chem. Soc.*, 1940, **62**, 1843.
[8] Bergmann and Bergmann, *ibid.*, 1940, **62**, 1699.

After several hours at room temperature, methanol (25 ml.) and sodium borohydride (1·5 g.) were added. After being kept overnight the mixture was worked up in the usual way and the product was obtained as a brown oil (1·25 g.). It gave no precipitate with 2 : 4-dinitrophenylhydrazine and its infrared spectrum exhibited no carbonyl absorption but showed a strong band at 3385 cm.$^{-1}$ (OH). (*b*) The oil was boiled with oxalic acid (0·5 g.) in toluene (50 ml.). A small amount of water was collected in the azeotropic adapter. After the usual working up an oil (1·2 g.) was obtained whose infrared spectrum showed no oxygen-containing functional groups. (*c*) The oil was heated under nitrogen with 30% palladised charcoal (200 mg.) at 310—320° for 1 hr. After cooling and extraction with hot benzene the catalyst was removed and the benzene solution was filtered through neutral alumina. Evaporation of the eluate gave chrysene, m. p. 252—255° (from toluene) (lit.,[9] m. p. 263—267°). It did not depress the m. p. of authentic chrysene, which in our hands had m. p. 253—255°.

No benz[*a*]anthracene was isolated from the dehydrogenations.

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[9] Wilds and Shunk, *ibid.*, 1943, **65**, 469.

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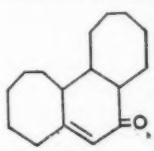
248. *Alicyclic Studies. Part IX.**
1 : 2 : 3 : 4 : 5 : 8 : 9 : 10 : 11 : 12-*Decahydrodi*cyclo*hepta*[a, c]*benzene.*

By WALTER J. ROSENFELDER and DAVID GINSBURG.

The preparation of 1 : 2 : 3 : 4 : 5 : 8 : 9 : 10 : 11 : 12-decahydrodi*cyclo*hepta[*a*, *c*]benzene is described.

1 : 2 : 3 : 4 : 5 : 6 : 8 : 9 : 10 : 11 : 12 : 5*a* : 12*a* : 12*b*-Tetradecahydro-6-oxodi*cyclo*hepta[*a*, *c*]-benzene (I) [1] has been reduced with sodium borohydride. Dehydration of the resulting allylic alcohol by several methods yielded a mixture of homoannular diene ($\lambda_{max.}$ 2740 Å) and heteroannular diene ($\lambda_{max.}$ 2450 Å). These maxima are analogous to the absorptions exhibited by cholesta-2 : 4- (2750 Å) and -3 : 5-diene (2340 Å), respectively.[2] Dehydrogenation of the mixture of dienes by bromination with *N*-bromosuccinimide followed by dehydrobromination with lutidine, or by heating with sulphur, yielded 1 : 2 : 3 : 4 : 5 : 8 : 9 : 10 : 11 : 12-decahydrodi*cyclo*hepta[*a*, *c*]benzene.



(I)

EXPERIMENTAL

Reduction of 1 : 2 : 3 : 4 : 5 : 6 : 8 : 9 : 10 : 11 : 12 : 5a : 12a : 12b-*Tetradecahydro-6-oxodi*cyclo*hepta*[a, c]*benzene*.—To a solution of the ketone (4 g.) in methanol (40 ml.), sodium borohydride (3 g.) was added gradually with shaking. After 1 hr. at room temperature, the solvent was removed at the water-pump. The residue was taken up in ether and washed with dilute hydrochloric acid and with water. After drying (Na_2SO_4) the ether was removed. The main fraction boiled at 160—170°/1·6 mm. The infrared spectrum showed a weak hydroxyl band at 3600 cm.$^{-1}$ but the ultraviolet absorption [$\lambda_{max.}$ 2450 Å (ε 2440 in EtOH)] indicated that considerable dehydration of the allylic alcohol had occurred.

Attempts to isolate the pure allylic alcohol by preparation of an acetate, benzoate, *p*-nitrobenzoate, 3 : 5-dinitrobenzoate, or phenylurethane, failed.

Preparation of Mixture of Dienes.—(*a*) The partially dehydrated allylic alcohol (10 g.) was refluxed in dry benzene (50 ml.) with naphthalene-β-sulphonic acid (0·5 g.), the water being removed in an azeotropic separator. Water removal was complete after 30 min. The solution was then washed with aqueous sodium hydrogen carbonate and with water, dried (Na_2SO_4), and distilled. The main fraction of dienes had b. p. 120—122°/0·5 mm. (Found : C, 88·8; H,

* Part VIII, preceding paper.

[1] Rosenfelder and Ginsburg, *J.*, 1954, 2955.

[2] Fieser and Fieser, "Natural Products related to Phenanthrene," Reinhold, New York, 1949, 3rd edn., p. 186.

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11·3. Calc. for $C_{16}H_{24}$: C, 88·8; H, 11·2%). Ultraviolet absorption: $\lambda_{max.}$ 2450, 2740 Å (ε 5150, 1750 in EtOH). The homoannular diene could not be isolated by means of a maleic anhydride adduct.

(*b*) The partially dehydrated alcohol (5 g.) and aluminium oxide (10 g.; 100-mesh, activated at 150° for 3 hr. and allowed to cool in a desiccator immediately before use) were heated at 170—180°/2 mm. for 1 hr. in a Claisen flask. The temperature was then raised to 200° and the product was distilled. The wet distillate was taken up in ether, and the ether layer separated, dried, and distilled. The main fraction of dienes distilled at 127—128°/1 mm. but the ultraviolet absorption spectrum indicated that some rearrangement to the heteroannular diene had taken place. Ultraviolet absorption: $\lambda_{max.}$ 2450, 2740 Å (ε 5100, 1750 in EtOH).

(*c*) Treatment of the partially dehydrated allylic alcohol (7 g.) in pyridine (30 ml.) with phosphorus oxychloride (7 g.) at 0°, followed by storage overnight at room temperature and working up in the usual way, gave a product which was still highly coloured after two high-vacuum distillations. Ultraviolet absorption: $\lambda_{max.}$ 2460 Å (ε 7100), indicating a high content of the heteroannular diene.

Reactions of the Mixture of Dienes.—(a) *With one mol. of N-bromosuccinimide.* To the diene mixture (12 g.) in dry carbon tetrachloride (100 ml.), *N*-bromosuccinimide (11·9 g., 1·1 mol.) was added with swirling and cooling during 10 min. An immediate vigorous reaction set in with some evolution of hydrogen bromide. To complete the bromination, the solution was heated under reflux for 10 min. After the usual working up, the residue was heated under reflux with lutidine (50 ml.) for 90 min. The solution was concentrated in a vacuum to 10 ml. and the lutidine hydrobromide was removed by filtration. This salt was washed with ether and the filtrate and washings were combined. The residual lutidine was removed by shaking five times with dilute hydrochloric acid and after three washings with water the ethereal layer was dried and distilled. After a small forerun, b. p. 138—143°/2·3 mm., the main fraction, b. p. 144—147°/2·3 mm. (6 g.), was obtained. Recrystallisation from ether–methanol gave large plates of 1:2:3:4:5:8:9:10:11:12-*decahydrodi*cyclo*hepta*[a, c]*benzene*, m. p. 56—57°. The analytical sample, m. p. 57—57·5°, was obtained by three recrystallisations from ether–methanol (Found: C, 89·7; H, 10·3. $C_{16}H_{22}$ requires C, 89·7; H, 10·3%). Ultraviolet absorption: $\lambda_{max.}$ 2600, 2690 Å (ε 321, 345 in heptane).

(b) *With sulphur.* A mixture of the dienes (6 g.) and sulphur (6 g.) was heated at 180°/25 mm. for 1 hr. The temperature of the metal-bath was then raised to 220°, material distilling at 184—186°/25 mm. The distillate was taken up in light petroleum (30 ml.), filtered from a little sulphur, and chromatographed on alumina (100 g.). On elution with light petroleum the first 100 ml. afforded merely traces, whereas the next 100 ml. gave 1:2:3:4:5:8:9:10:11:12-decahydrodi*cyclo*hepta[*a*, *c*]benzene (2·3 g.), plates, m. p. and mixed m. p. 56—57° (from ether–methanol). Further elution with light petroleum gave only traces of material.

(c) *With selenium.* A mixture of the dienes (10 g.) and selenium (15 g.) was heated for 2 hr. at 200°, and the temperature was then raised during 1 hr. to 345°. This temperature (±5°) was maintained for 24 hr., the product was cooled, and the solid mass was repeatedly extracted by heating under reflux with benzene. The benzene extract was concentrated in a vacuum and filtered through a column of alumina (200 g.) to remove most of the selenium. Upon distillation, the product (8·4 g.) had b. p. 146—150°/3 mm. Redistillation from sodium gave the analytical sample, b. p. 146—148°/4 mm., n_D^{25} 1·5255 (Found: C, 88·0; H, 11·5%). The analytical figures indicate that disproportionation may take place and the oil isolated is a more reduced product. A more dehydrogenated product was not isolated. Kuhn–Roth determination showed no rearrangement to a product containing *C*-methyl groups had occurred and no absorption at 1375 cm.$^{-1}$ was found in the infrared spectrum of the product.

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249. *The Szilard–Chalmers Reaction in Ethyl Bromide.*

By Miriam Milman and P. F. D. Shaw.

The nature of the reactions following neutron capture by the bromine atom in ethyl bromide has been investigated by analysing the products at different free bromine concentrations. The products from the processes associated with the slowing down of the energetic atoms consist largely of compounds which could only be produced from highly fragmented ethyl bromide molecules. By contrast, the product from the ensuing diffusion-dependent reactions consists only of ethyl bromide.

When organic halides are irradiated with neutrons, part of the radio-halogen produced can be extracted with an aqueous reagent, and part remains in organic combination. This effect, first observed by Szilard and Chalmers,[1] occurs because, after neutron capture, the radiation emitted by a halogen atom may impart to it a recoil energy of the order of tens of electron volts. The parent molecule therefore dissociates, and, in the ensuing chemical reactions, the radioactive atom may form inorganic or new organic species (see, for example, Glückauf and Fay [2]). The most recent reviews of the work of several investigators who have attempted to determine the nature of these reactions are by Willard.[3,4]

One of the first attempts to account for the distribution of the active halogen atoms among the new chemical species was Libby's " billiard-ball hypothesis." [5] In this it was assumed that recoiling atoms lose their energy by elastic collisions with neighbouring atoms, which were regarded as free; this seemed plausible since the chemical binding energies of atoms in molecules are small compared with the recoil energy. In these circumstances, the only single collisions capable of reducing the high energy of the recoiling atoms to the thermal region are " head-on " collisions with other (halogen) atoms having approximately the same mass, whereupon the recoil energy is transferred to an inactive atom which is projected from the site of the collision; the de-energised radio-halogen atom is thus left in a liquid " cage " with the radical to which the inactive atom was originally joined. The ensuing combination must therefore result in the formation of a molecule of the parent compound, and the theory successfully accounted for the large percentage of the activity present in the parent compound (cf. refs. 2 and 6).

Glückauf and Fay [2] and Fox and Libby [6] also found that among the new organic compounds produced those formed by substitution of bromine in the original compound predominated. To account for this, Libby and his co-workers [6,7] postulated that, when the energy of the recoiling atom was reduced by collision to a few electron volts, whole molecules could be activated by inelastic collisions which caused rupture of C–H bonds and combination of the organic radical with the de-energised radio-halogen atom.

An account of the criticisms of this theory has been given by Willard.[3] For present purposes, one of the most important of these is the implausibility of the assumption that the collisions can be treated as elastic when the recoiling atom has a high energy. This can be simply illustrated for a molecule such as ethyl bromide by considering a collision in the direction of a C–Br bond such that the bromine atom is caused to move towards the carbon. Since the whole molecule is confined by the walls of the liquid [8] the C–C bond must be considerably activated and might dissociate. Evidence for such activation has

[1] Szilard and Chalmers, *Nature*, 1934, **134**, 462.
[2] Glückauf and Fay, *J.*, 1939, 1273.
[3] Willard, *Ann. Rev. Nuclear Sci.*, 1953, **3**, 193.
[4] *Idem*, *ibid.*, 1955, **6**, 141.
[5] Libby, *J. Amer. Chem. Soc.*, 1947, **69**, 2523.
[6] Fox and Libby, *J. Chem. Phys.*, 1952, **20**, 487.
[7] Friedman and Libby, *ibid.*, 1949, **17**, 647.
[8] Cf. Franck and Rabinovitch, *Trans. Faraday Soc.*, 1934, **30**, 120.

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been given by Collie and Shaw [9] who found that methylene dibromide was produced in neutron-irradiated ethyl bromide.

Willard and his colleagues [10, 11] have suggested as an alternative theory that the reactions of halogen atoms following neutron capture occur in two stages. In the first the recoiling (highly energetic) atom loses energy by inelastic collisions producing a large local concentration of molecular fragments (free radicals and inorganic atoms); the active atom might then combine with one of these when it has lost sufficient energy, thus producing organic or inorganic molecules. After losing its energy, the active atom, together with some of the free radicals produced, diffuses into the surrounding liquid. After many collisions with solvent molecules these radicals might combine among themselves, or with the active atom, until the system becomes so dispersed by diffusion that the probability of such reactions is negligible. In this and the following papers, reactions occurring in the first stage are termed " high-energy reactions " (after Willard [3]), and those in the second stage diffusion-dependent or " diffusive " reactions.

This theory succeeds in accounting for the disproportionately large drop in retention (defined as the fraction of the total activity produced which is present in organic combination) found when small quantities of elementary halogen are present in the halide during irradiation. This effect was discovered by Lu and Sugden,[12] and has been investigated by others, particularly Willard and his colleagues,[10, 11] who also found that as the halogen concentration is further increased, the retention becomes relatively insensitive to change in it. The initial sharp decrease in retention was ascribed to the removal, by reaction with the added halogen, of organic radicals which might otherwise react with the active atom in the diffusion-dependent stage. When the halogen concentration is sufficiently great, the formation of organic halides by such processes can be made negligible, and the radioactive organic compounds present are then those produced predominantly by combination of the active atom with a radical in the initial (high energy) stage.

Proof that bromine atoms are involved in the processes following neutron capture in ethyl bromide has been given by Goldhaber and Willard [10] and Roy, Williams, and Hamill [13] who added small quantities ($\sim 10^{-3}$ molar fraction) of 1 : 2-dibromoethylene to the liquid before irradiation; the retention was increased from 32 to 60%. Since 1 : 2-dibromoethylene exchanges readily with bromine atoms,[14] this shows that 28% of the radiobromine produced ultimately enters inorganic combination by thermal processes; the remaining 40% of the inorganic active bromine is attributed to molecules produced in the high-energy stage.

No attempt has been made to determine the nature of the reactions occurring in either the diffusion-dependent or high-energy stages. In the latter, the radicals available for combination with the active atom might consist of extremely unstable molecular fragments, di-radicals, etc., since considerable energy has been dissipated among relatively few molecules. The compounds produced by combination of the active atom with one of these should therefore indicate how far solvent molecules are disrupted by the recoiling atom; for example, methylene dibromide formed from radicals (made by breaking the C–C bonds in ethyl bromide) might be produced predominantly in the high-energy stage. During the slower diffusive stage, however, highly unstable fragments might disproportionate or react with solvent molecules to form more stable radicals, so that the compounds formed by combination with the active atoms would differ chemically from those from the first stage.

We now give an account of an investigation of the nature of the products formed in the two groups of reactions following neutron capture by bromine in ethyl bromide.

[9] Collie and Shaw, *J. Chim. phys.*, 1951, **48**, 198.
[10] Goldhaber and Willard, *J. Amer. Chem. Soc.*, 1952, **74**, 318.
[11] Levey and Willard, *ibid.*, p. 6161.
[12] Lu and Sugden, *J.*, 1938, 1273.
[13] Roy, Williams, and Hamill, *J. Amer. Chem. Soc.*, 1954, **76**, 3274.
[14] Williams, Hamill, Schwartz, and Burell, *ibid.*, 1952, **74**, 5737.

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Retentions in Pure Ethyl Bromide.—Earlier figures for the retentions in this substance [15, 16, 17] are considerably greater than that (32%) obtained by Goldhaber and Willard [10] in specimens carefully purified by different methods. The last authors ascribed the earlier high values to the effects of impurities capable of returning the inorganic radiobromine to organic combination.

In the present work the ethyl bromide was purified by two methods, one of which was identical with one used by Goldhaber and Willard; if the period of irradiation was greater than about four days the ethyl bromide became yellow owing to elementary bromine, and the observed retentions agreed with those found by the last authors. It is possible (cf. ref. 18) that the bromine might have been formed by the action of gamma-rays on the

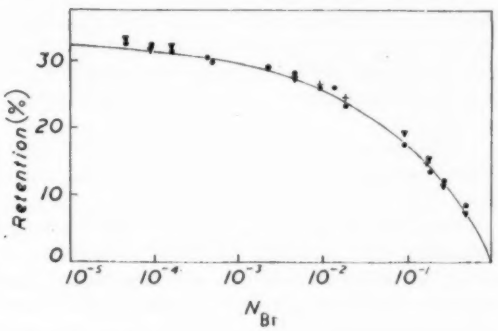

FIG. 1. *Retention o, ethyl bromide as a function of the molar fraction of bromine.*
+ ^{80}Br; ● ^{80}Br*; ▼ ^{82}Br.

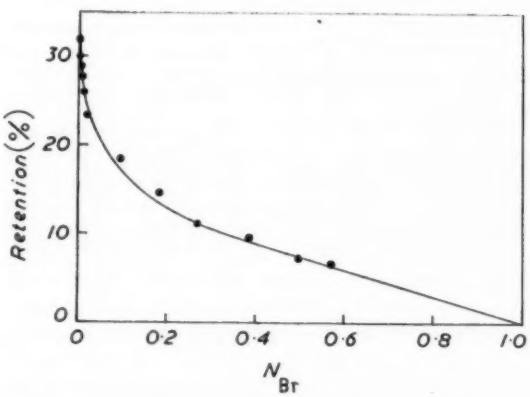

FIG. 2. *Retention of ethyl bromide as a function of the molar fraction of bromine. The points shown are the weighted mean of the values, given in Fig. 1, taken at the same molar fraction of bromine.*

ethyl bromide in the presence of oxygen, which was not excluded in our work. However, for shorter irradiations the retentions found were variable and significantly greater (35—39%). Attempts were made to see whether this could be caused by the effects of impurities such as those postulated by Goldhaber and Willard, by observing the retention found by extraction 12 hrs. after removal of the ethyl bromide from the neutron source. During this period the specimens were kept either in darkness or near a 500 mc radium source to simulate the γ-ray flux from the Ra–Be neutron source. No transfer of the activity from the inorganic to the organic fraction was observed, and it is therefore improbable that the greater retentions could be produced by reaction with impurities.

[15] Libby, *J. Amer. Chem. Soc.*, 1940, **62**, 1930.
[16] Hamill, Williams, Schwartz, and Voiland, University of Notre Dame Radiation Chemistry Report, March 1st, 1951; quoted in ref. 10.
[17] Shaw and Collie, *J.*, 1951, 434.
[18] Chien and Willard, *J. Amer. Chem. Soc.*, 1955, **77**, 3441.

Possible explanations of this effect are given in the Discussion. For present purposes the discrepancy between our results and those of Goldhaber and Willard is not unduly disturbing since, by the addition of small quantities of inactive bromine (10^{-5} molar fraction), the retentions were stabilised and agreed with those quoted for similar conditions by them.[10]

Retentions with Bromine Present.—By extrapolating the less sensitive part of the plot of retention against bromine concentration it is possible to obtain a value for the retention due to high-energy processes at zero bromine concentration. Its value in ethyl bromide has been reported as 25%[10] and 20%.[13] In view of this discrepancy, the retentions of ethyl bromide as a function of bromine concentration were re-determined, the concentration of bromine being varied over a greater range than that used previously. The results are shown in Figs. 1 and 2; the purpose of the semi-logarithmic plot is to show more clearly the retentions obtained at low concentrations. Fig. 2 shows that the initial fall of the curve at low bromine concentration gives way to an almost linear portion which can be extrapolated to retentions of 0 and 15% at 1 and 0 molar fraction of bromine respectively.

The retentions found for the three isotopes of bromine produced (^{80}Br, ^{80}Br*, and ^{82}Br; half-lives 18 min., and 4·5 and 35 hr. respectively) are the same within experimental error (Fig. 1), in agreement with previous observations [6, 7, 19] with other aliphatic bromides.

Analysis of the Products from Neutron-irradiation.—The active products from ethyl bromide were analysed at two concentrations of elementary bromine; the results are given in the Table, in which the percentage activities of the fractions are the weighted mean of the results obtained for ^{80}Br* and ^{82}Br, which were identical within the statistical error of counting.

	N_{Br}		(*c*) Ratio :	Activity at $N_{Br} = 0$ due to	
	(*a*) $8·9 \times 10^{-5}$	(*b*) 0·27	% activity in (*a*) / % activity in (*b*)	(*d*) High-energy processes	(*e*) Diffusive processes
Retention	31·47 ± 0·49	12·75 ± 0·29	—	—	—
Ethyl bromide	22·60 ± 0·38	6·03 ± 0·18	3·75 ± 0·13	8·25 ± 0·25 (5·79) *	14·35 ± 0·45 (16·81) *
Methylene dibromide...	2·21 ± 0·06	1·27 ± 0·04	1·74 ± 0·07	1·74 ± 0·05	0·47 ± 0·08
Ethylidene dibromide	1·87 ± 0·09	0·91 ± 0·10	2·06 ± 0·25	1·24 ± 0·14	0·63 ± 0·17
Ethylene dibromide ...	1·04 ± 0·05	0·70 ± 0·11	1·49 ± 0·25	0·96 ± 0·15	0·08 ± 0·16
Bromoform	0·56 ± 0·03	0·51 ± 0·03	1·10 ± 0·09	0·70 ± 0·04	−0·14 ± 0·05
Tribromoethane	0·86 ± 0·07	1·04 ± 0·05	0·83 ± 0·08	1·42 ± 0·07	−0·56 ± 0·10
Tetrabromoethane (residue)	0·32 ± 0·04	0·24 ± 0·03	1·33 ± 0·18	0·32 ± 0·04	0·00 ± 0·06

* Corrected values : See Discussion.

The errors given in this Table, and those in the following papers, are the standard deviations derived from the counting statistics.

Experiments were performed to confirm that no exchange occurred between the fractions during their separation by fractional distillation, in agreement with Rowland and Libby's observation,[20] but it was found that with normal separation procedure an error was introduced owing to incomplete separation of the neighbouring fractions. This was probably about 2—3% of the activity of these fractions; *e.g.*, for the experiment in column (*a*) in the Table the error in the bromoform fraction due to poor separation could be as much as 3% of (1·04 + 0·86), the percentage activities of the neighbouring ethylene dibromide and tribromoethane fraction. The errors quoted, which are those due to the statistics of counting, should therefore be increased by this amount.

The results differ from those obtained by Collie and Shaw [17] with less rigorously purified material. Their results were undoubtedly influenced by impurities, as suggested by Willard.[3] Preliminary experiments, not described here, have shown that the presence

[19] Chien and Willard, *J. Amer. Chem. Soc.*, 1954, **76**, 4735.
[20] Rowland and Libby, *J. Chem. Phys.*, 1953, **21**, 1495.

of sulphur dioxide (a possible impurity from sulphite extraction) in ethyl bromide causes results similar to those found earlier.

Discussion

The retentions in pure ethyl bromide found in the present work are greater than those found by Goldhaber and Willard.[10] This could be explained if the high γ-ray flux (from a 3c Sb–Be source) used in their experiments produced bromine more rapidly than that from the 500 mc Ra–Be source used by us. Alternatively, the greater retentions might be due to reactions in which inorganic bromine is returned to organic combination; since no evidence for these could be found in a γ-ray flux comparable with that associated with the neutron irradiation, these reactions could only be initiated by neutrons. Owing to the greater energy of the neutrons from the Ra–Be (than the Sb–Be) source, a small stationary concentration of organic radicals may be produced by protons from (n,p) scattering. If this were so, higher retentions might be caused by reactions of the type:

$$R + BrBr^* \longrightarrow RBr^* + Br$$

Very small concentrations of inactive bromine would suffice to reduce the concentration of such radicals to negligible proportions.

It is also possible that the purity obtained by us was less than that obtained by Goldhaber and Willard, but the reasonable consistency of the retentions (35—39%) obtained in differently purified specimens makes this explanation improbable.

The linear form of Fig. 2 at high bromine concentrations is consistent with the interpretation that in this region the retentions are predominantly produced by high-energy processes, since the probability of a recoiling atom's forming an organic bromide at this stage should be proportional to the concentration of organic radicals in the vicinity of the recoil "track." Since such radicals can only be produced from ethyl bromide molecules, it would be expected that R_E, the retention due to high-energy processes, would be proportional to $(1 - N_{Br})$ (where N_{Br} is the molar fraction of bromine present). The value (15%) of R_E obtained by extrapolation to zero bromine concentration is lower than that obtained by Goldhaber and Willard [10] or by Roy *et al.*; [13] however, this was expected since the measurements by these authors covered only a small range of bromine concentration, a fact which might also explain the discrepancy between their values for R_E.

On this interpretation, the ratio of R_E at $N_{Br} = 0$ to that found at $N_{Br} = 0{\cdot}27$ is 1·37 $[1/(1 - 0{\cdot}27)]$. For the results given in the Table, the corresponding ratio for those products whose formation is by high-energy processes should also be the same, and compounds which are produced in the diffusion-dependent processes should show a ratio greater than this. Column (*c*) shows these ratios for the individual fractions; the greatest ratio is that found for ethyl bromide, indicating that a large proportion of this fraction is produced by diffusion-dependent reactions. If it is assumed that, at $N_{Br} = 0{\cdot}27$, only high-energy processes are responsible for the production of the active organic bromides, it is possible to estimate the yields of individual fractions from such processes occurring at $N_{Br} = 0$; the values obtained are given in column (*d*), and were found by multiplying the figures in (*b*) by 1·37.

The activities obtained by subtracting the figures in column (*d*) from those in (*a*) should now give an estimate of the diffusion-dependent yields of the individual fractions [column (*e*)]. Since the total yield expected from such processes is 17% (= 32 − 15), it can be seen that the predominant product is ethyl bromide.

The negative values in column (*e*) probably mean that the yields of these fractions are not reliable. They could arise if active compounds, for which no carriers were added, were present in the irradiated ethyl bromide, since these might appear with the carrier fractions in variable amount. Support for this can be obtained from the fact that the sums of the individual fractions in (*a*) and (*b*) are less than the total observed retentions,

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indicating that loss of activity, for which no correction was made, occurred during the fractional distillation.

The ethyl bromide fractions are unlikely to be subject to the same error, since we had sufficient to allow more generous rejection of the first and last fractions during the distillation.

The arguments above are based on the assumption that the total organic yield at $N_{Br} = 0{\cdot}27$ is from high-energy reactions; if this were so, the retention would be only 10·95%, whereas that found was 12·75%. The difference (1·80%) is probably due to the occurrence of diffusion-dependent reactions, and this therefore indicates that the true yield of ethyl bromide from high-energy processes should be approximately (6·03 — 1·80) = 4·23%. Using this modified value, and performing the above operations, we find that the yields of ethyl bromide at $N_{Br} = 0$ from the two sets of reactions are 5·79 and 16·81%, the latter being almost exactly equal to the graphical estimate for the total activity produced by diffusive reactions.

The experiments therefore support the hypothesis [10, 11] that the reactions occur in two stages. By use of the extrapolation technique of Goldhaber and Willard [10] and Roy *et al.*[13] it has been possible to show that probably the entire yield from diffusion-dependent reactions consists of ethyl bromide, the other active products bring produced by high-energy reactions. This is consistent with the view that the products from the initial stage should be more complex than those from the final stage. The degree to which molecular fragmentation occurs may be surmised from the formation of substances, such as methylene bromide or bromoform, which indicates that C–C bonds are broken, and that possibly fragments as small as :CHBr are produced; for example, such a radical could add bromine to form bromoform or combine with a similar radical to give dibromoethylene, subsequent saturation of which could give tetrabromoethane. However, in view of the difficulty in reproducing the activities in such fractions the interpretation of such processes must remain highly speculative, needing a more substantial experimental basis than that here provided.

The formation of ethyl bromide in the diffusion-dependent reactions could be by any of the following:

$$C_2H_5\cdot + Br^* \longrightarrow C_2H_5{\cdot}Br^* \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (A)$$

$$C_2H_5\cdot + BrBr^* \longrightarrow C_2H_5{\cdot}Br^* + Br \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (B)$$

$$\text{or } C_2H_5{\cdot}Br + Br^* \longrightarrow C_2H_5{\cdot}Br^* + Br \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (C)$$

Reaction (*C*) may be neglected, because its activation energy is prohibitively high [21] (25 kcal./mole) for the thermal atom involved, and it has been shown [10, 13] that active bromine atoms, diffusing from the site of their formation, normally form inorganic compounds. The relative importance of reactions (*A*) and (*B*) is discussed in more detail later,[22] but it is noteworthy that both involve ethyl radicals. From the relative activities of the fractions produced in the high-energy processes it appears that unless reaction (*C*) is important in this case, approximately one half of the radicals involved are ethyl radicals, the others being " complex." Since none of the latter exists for sufficient time to play an observable part in the thermal processes, which involve only simple ethyl radicals, it is probable that they form ethyl radicals by removal of bromine atoms from solvent molecules.

Experimental

Purification of Ethyl Bromide.—(i) Ethyl bromide (British Drug Houses Ltd.) was distilled and then stored in daylight with elementary bromine to remove olefins. It was then shaken with dilute sodium sulphite solution, separated, and dried ($CaCl_2$); the liquid was then distilled in a column (40 cm. × 1·5 cm. diam.) packed with glass helices, the middle 50% being retained.

[21] Liberatore and Wiig, *J. Amer. Chem. Soc.*, 1940, **8**, 349.
[22] Milman and Shaw, *J.*, 1957, 1317.

(ii) As in ref. 11, after preliminary distillation, the ethyl bromide was shaken with concentrated sulphuric acid, then washed several times with dilute sodium carbonate solution, and finally with distilled water. After being dried ($MgSO_4$) it was fractionally distilled as above.

Technique.—Neutron irradiations were performed in darkness by placing standard 50 ml. flasks containing ethyl bromide round a 500 mc Ra–Be source held centrally in a trough of water made from paraffin wax. It was found that the retentions of samples containing $N_{Br} = 10^{-5}$ were unaffected by the distance from the source and no rigorous precautions were taken to ensure constant geometry.

Extractions were made by shaking a portion of irradiated ethyl bromide with dilute sodium sulphite solution containing sodium bromide as carrier. After separation, the liquid was dried ($CaCl_2$) and a little elementary bromine was added. The unextracted portion was poured into a fresh flask and a little bromine added to ensure that any inorganic ^{80}Br produced by decay of $^{80}Br^*$ did not settle on the walls of the containing flask or the counter. The irradiation-flask was washed out with sodium bromide solution which was then treated with chlorine; the bromine produced, together with excess of chlorine, was successively extracted with carbon tetrachloride. The activity of this was measured to ensure that none of the active inorganic species had been absorbed on the walls during irradiation, since otherwise a spurious value for the activity of the unextracted fraction would result.

All measurements were made on liquid samples with an M.6 counter (Twentieth Century Electronics Ltd.). In experiments on ^{80}Br (half-life 18 min.), the period of irradiation was only 10—15 min., and the activities of the different fractions were measured as soon as possible. The activity was again measured 4 hr. later to determine to what extent activity from $^{80}Br^*$ had contributed to the first measurement; this was negligible unless the period between removal from the source and the first measurement was very long. For experiments with $^{80}Br^*$ and ^{82}Br the period of irradiation was greater than 15 hr. At least 4 hr. were allowed to elapse between extraction and measurement to ensure that ^{80}Br, directly produced by neutron capture, had decayed to negligible proportions, and to allow the establishment of transient equilibrium between $^{80}Br^*$ and ^{80}Br. A further measurement was made 15 hr. after the first, thus enabling the determination of the activities due to $^{80}Br^*$ and ^{82}Br. Any activity obtained from the walls of the irradiation flask was corrected for dilution, and also for the greater density of carbon tetrachloride than of ethyl bromide by using an empirically determined "self-absorption" curve.

The yellow colour produced on neutron irradiation was shown to be due to bromine by its disappearance on shaking with sulphite, and by the liberation of iodine from starch–iodide paper; freshly prepared ethyl bromide did not react with the latter. For specimens held near the Ra–Be source, 10^{-5} molar fraction of bromine, determined by colorimetric matching with standards, was produced by five days' irradiation.

The absence of reactions capable of producing organic bromides from the extractable radiobromine was checked by irradiating a specimen for 15 hr. This was divided into three aliquot parts; one was extracted immediately after removal from the source, and the others were left for 12 hr. in darkness, one near 500 mc of radium and the other in a place free from radiation. They were then extracted; in both cases the rate of loss of radiobromine from the inorganic fraction (fraction lost per hour) was $0 \pm 0{\cdot}0012$, the retention for $^{80}Br^*$ being 35·1%.

Retentions with Bromine Present.—The extractions were performed with sodium sulphite solutions of appropriate concentration. For the extraction of the more concentrated solutions of bromine, the sulphite solution was cooled with a slurry of ice, to prevent evaporation of the ethyl bromide by the heat of reaction between the bromine and sulphite. Counts were made as already described, and were corrected for the differing densities and also for the volume of bromine used. For example, if a certain solution contained A ml. of ethyl bromide and B ml. of bromine, then C ml. of the unextracted solution contained $CA/(A + B)$ ml. of ethyl bromide; in order to compare its activity with that of C ml. of extracted ethyl bromide, the activity of the former therefore had to be multiplied by the factor $(A + B)/A$.

Analysis of the Products from Neutron-irradiation.—100 ml. samples of ethyl bromide containing bromine were irradiated for five days; 12 ml. were retained for measurement of the total activity, the rest being extracted. To 50 ml. of the latter were added 10 ml. portions of methylene, ethylidene, and ethylene bromide and bromoform, and 5 ml. of 1 : 1 : 2-tri- and 1 : 1 : 2 : 2-tetra-bromoethane (all from British Drug Houses Ltd., distilled). The mixture was re-extracted to remove any bromine which might have been present in the carriers.

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After being dried ($CaCl_2$), the mixture was separated into its consitutents by fractional distillation in a column packed with glass helices and purposely made small (20 cm. × 1·5 cm.) to ensure small hold-up. Ethyl bromide and methylene and ethylidene dibromide were collected at atmospheric pressure, the remaining carriers being separated under reduced pressure. As a check on the purity of each fraction, the boiling and condensing temperatures were taken, the fraction being re-distilled if these temperatures differed by more than about 0·2°; this criterion was not applied to the tetrabromoethane fraction which was recovered as the residue in the distilling flask. The volumes of the various fractions recovered pure (about 2—3 ml.) were measured, and made up to 11 ml. with carbon tetrachloride. The activities of each fraction were corrected for losses occurring during the fractionation and for the density of the resulting carbon tetrachloride solution.

The use of bromoform as a carrier was suggested by its production on neutron-irradiation of methyl bromide [23] and by the formation of iodoform (1%) in irradiated methyl iodide.[24]

In order to check that no exchange occurred between the fractions during the distillation, ethylene dibromide labelled with ^{82}Br was mixed with the remaining carriers, and separated as above. After applying the above corrections it was found that 96% of the active material was recovered as ethylene dibromide, the remaining activity being distributed between the ethylidene dibromide (1·6%) and bromoform (2·8%) fractions. By adding more (inactive) ethylene dibromide to the latter fractions it was shown that their activity was caused by the presence of ethylene dibromide, and was not produced by exchange.

The authors are indebted to Prof. Lord Cherwell, F.R.S., for laboratory facilities.

THE CLARENDON LABORATORY, OXFORD. [*Received, July 7th*, 1956.]

[23] Hazelwood, personal communication.
[24] Shaw, unpublished results.

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250. *The Szilard–Chalmers Reaction in Ethylene Dibromide.*

By MIRIAM MILMAN, P. F. D. SHAW, and I. B. SIMPSON.

The retentions of radio-bromine produced by neutron capture in purified ethylene dibromide are not reproducible. This can be largely explained by the presence of vinyl bromide which is formed, on storage and by radiolysis, by dissociation of the parent compound. When present, vinyl bromide causes increased retentions by exchanging with radio-bromine atoms produced by neutron capture; subsequent addition of bromine or hydrogen bromide gives increased yields of active tribromoethane or ethylene dibromide respectively.

Analysis of the products from the neutron irradiation of bromine–ethylene dibromide mixtures, shows that the predominant diffusion-controlled reactions result in the formation of ethylene dibromide and vinyl bromide, which is subsequently saturated to give tribromoethane.

THE work described earlier [1] supports the suggestion of Willard and others [2,3] that the reactions following neutron capture in ethyl bromide occur in two stages. A considerable fraction of the high-energy products consisted of ethyl bromide; according to Libby's [4] "billiard ball" hypothesis (see p. 1203), a high yield of the parent substance would be expected. Although Libby's theory is subject to criticism, since most collisions by the recoiling atom are inelastic, it is possible that some collisions between the recoiling atom and a bound bromine atom might result in relatively little activation of the group attached to the struck atom, and in these conditions a high yield of the parent compound might be produced. Since such processes could only occur when Br–Br collisions are involved,[4] substances containing a greater number of bromine atoms per carbon atom than ethyl bromide should give an increased yield of the parent compound from the high-energy

[1] Milman and Shaw, preceding paper.
[2] Goldhaber and Willard, *J. Amer. Chem. Soc.*, 1952, **74**, 318.
[3] Levey and Willard, *ibid.*, p. 6161.
[4] Libby, *ibid.*, 1947, **69**, 2523.

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reactions. In order to investigate this, and also to see whether the production of the parent compound from the second (diffusive-recombination) stage is a general feature of the Szilard–Chalmers effect in aliphatic bromides, a study similar to that for ethyl bromide was made with ethylene dibromide.

The Szilard–Chalmers effect in ethylene dibromide has been relatively little investigated. Shaw and Collie [5] found difficulty in obtaining reproducible results, and preliminary experiments indicated that the processes following neutron capture were more complex than those occurring in ethyl bromide.

Retention in Pure Ethylene Dibromide.—As no reproducible results were obtained for the retention in this compound, experiments were generally performed in pairs by using two portions of the same specimen and varying a single parameter likely to influence the retention. The retentions obtained were greater for ^{82}Br (half-life 35 hr.) than for ^{80}Br* (4·4 hr.). As the retentions in pure substances are the same for all the bromine isotopes,[6-8] this suggested the occurrence of slow reactions capable of returning the inorganic radiobromine to the organic fraction. Such effects have been observed [7] in impure substances, and in bromobenzene [9] where a γ-ray induced exchange occurs between elementary bromine and bromobenzene.

Shaw and Collie,[5] using less carefully purified ethylene dibromide, observed slow reactions of this type and suggested that exchange between active hydrogen bromide and ethylene dibromide might occur. To test this, hydrogen [^{82}Br]bromide was passed into ethylene dibromide, and the solution kept near a 500 mc Ra–Be neutron source for eight days. If it is assumed that the activity in the organic fraction was produced by exchange, the observed rate was much too small to account for the difference in retention between the isotopes, and another explanation was sought.

Early in this work, the retentions in purified ethylene dibromide were found to increase with the time elapsing between purification and extraction. This was most pronounced when the samples were kept either near the neutron source or in daylight, and suggested that an impurity from the decomposition of the ethylene dibromide was introduced. Dissociation into vinyl and hydrogen bromide, which occurs readily [10] at 350°, might occur at room temperature to yield sufficient vinyl bromide to react with the elementary bromine formed by neutron capture to give tribromoethane. To test this explanation, a freshly purified ethylene dibromide sample was split into two portions, to one of which a small quantity of vinyl bromide was added. The retentions found [Table 1, (*a*) and (*b*)] showed the expected increase when vinyl bromide was present, the fractions chiefly affected being vinyl bromide, ethylene dibromide, and tetrabromoethane. The last was recovered as a residue from the separation, and might therefore also contain higher-boiling compounds. In view of the sensitivity of the retention to the presence of vinyl bromide, experiments were always performed with fresh samples of ethylene dibromide, specimens to which vinyl bromide had been added, either before or after irradiation (as carrier), being permanently discarded.

Williams, Hamill, and Schwartz [11,12] have shown that rapid exchange occurs between bromine atoms and a number of vinylic compounds containing bromine. Small quantities of 1 : 2-dibromoethylene added to ethyl bromide before irradiation increase the retention from 32 to 60%; [2,13] this increase has been interpreted to mean that 28% of the radiobromine atoms produced escape from the site of their formation as atoms, thus enabling exchange with the dibromoethylene.

[5] Shaw and Collie, *J.*, 1951, 434.
[6] Fox and Libby, *J. Chem. Phys.*, 1952, **20**, 487.
[7] Rowland and Libby, *ibid.*, 1953, **21**, 1495.
[8] Chien and Willard, *J. Amer. Chem. Soc.*, 1954, **76**, 4735.
[9] Milman and Shaw, *J.*, 1956, 2101.
[10] Iredale and Maccoll, *Nature*, 1937, **140**, 24.
[11] Hamill and Williams, *J. Amer. Chem. Soc.*, 1950, **72**, 2813.
[12] Hamill, Williams, and Schwartz, *ibid.*, p. 2813.
[13] Roy, Williams, and Hamill, *ibid.*, 1954, **76**, 3274.

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On irradiating ethyl bromide containing 10^{-3} molar fraction of vinyl bromide, a retention of 60% was obtained, indicating that a similar exchange occurs with vinyl bromide. This might partly account, therefore, for the large activity in this fraction observed throughout the results shown in Table 1. The increased activity of the ethylene dibromide fraction when vinyl bromide was present could be explained by addition of hydrogen bromide. By comparison with the smaller ethylene dibromide activity found

TABLE 1.

	(*a*) Containing $5{\cdot}5 \times 10^{-5}$ molar fraction of vinyl bromide		(*b*) As (*a*), but no vinyl bromide		(*c*)	(*d*) Same specimen as (*c*)		(*c*)	(*f*) Same specimen as (*e*)	
Irradiation time	11 d.		10 d.		21·8 hr.	16 d.		14·9 hr.	5 d.	
Bromine isotope	$^{80}Br^*$	^{82}Br	$^{80}Br^*$	^{82}Br	$^{80}Br^*$	$^{80}Br^*$	^{82}Br	$^{80}Br^*$	$^{80}Br^*$	^{82}Br
Vinyl bromide	16·10	11·71	7·46	7·20	12·31	5·85	5·00	4·00	9·92	7·29
Methylene dibromide...	5·85	2·22	5·40	3·81	4·30	5·44	1·91	3·07	3·96	2·78
Ethylidene dibromide	4·87	3·51	3·42	3·10	3·92	4·61	2·81	1·37	3·81	3·24
Ethylene dibromide ...	27·90	31·02	20·62	24·81	28·75	23·30	29·00	16·71	21·85	36·42
Bromoform	5·51	6·51	3·67	4·40	6·26	4·82	8·06	3·54	3·71	11·01
1 : 1 : 2-Tribromoethane	4·81	6·40	3·94	6·47	11·48	5·14	6·74	2·36	3·62	8·24
1 : 1 : 2 : 2-Tetrabromoethane (residue)	8·64	11·75	3·76	6·71	9·49	3·32	5·76	1·34	3·49	9·75
Observed retention ...	69·40	70·04	55·5	64·61	79·45	52·52	66·21	35·52	51·45	72·58

Specimens (*a*), (*b*), (*c*), and (*d*) were pre-treated by boiling off a small quantity of ethylene dibromide before irradiation; only specimen (*a*) contained added vinyl bromide. Specimens (*e*) and (*f*) were purified by fractional crystallisation. The standard deviations due to counting were approximately 2—3% for $^{80}Br^*$ and 5—8% for ^{82}Br.

when small quantities of elementary bromine were present during the neutron irradiation [Table 2, (*a*)], it appears that such addition must occur in nearly all specimens of purified ethylene dibromide.

In order to determine the conditions under which vinyl bromide might be produced by the decomposition of ethylene dibromide, a sample of the latter was refluxed in daylight in a closed system at 131°; after 20 days the first fraction distilling from the ethylene dibromide was collected in a freshly purified sample, and the mixture irradiated simultaneously with another portion of the pure specimen. The retention for $^{80}Br^*$ in the latter (44%) was less than that in the mixture (55%); an analysis was made after adding a trace of elementary bromine and allowing the solution to stand in daylight to saturate vinyl bromide present. The difference in retention (10%) was reflected in the increased yields of ethylene dibromide (3·7%) and tribromoethane fractions (7·2%), and the results were therefore consistent with the presence of vinyl bromide in the products from the boiled specimen.

The variation of retention with the time near the neutron source was also investigated; the results from two sets of experiments are given in Table 1 [experiments (*c*) and (*d*), and (*e*) and (*f*)]. They are apparently erratic, the retentions increasing with time when the initial concentration of vinyl bromide (as indicated by the activity in this fraction for short irradiations) was small, and decreasing for larger initial concentrations. This effect was also observed in other (unpublished) experiments. The ethylene dibromide used in experiments (*e*) and (*f*) was probably purer than that used in (*c*) and (*d*), since the final purification consisted of fractional crystallisation in darkness, thus avoiding heat treatment.

Further, when active bromine is added to ethylene dibromide previously subjected to the action of daylight or γ-rays, a large part of the activity is found in the tetrabromoethane (residue) fraction, approximately half the activity of which was present as high-boiling compounds. This, together with the fact that vinyl bromide polymerises in daylight suggests that polymerisation of vinyl bromide might also affect the ultimate distribution of activity in purified ethylene dibromide.

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Retentions in Bromine–Ethylene Dibromide Mixtures.—Values of these are plotted against bromine concentration in the Figures. It was difficult to obtain reproducible results when only small quantities of bromine were present, since it was sometimes lost during irradiation. Addition of elementary [^{82}Br]bromine showed that the loss of bromine was accompanied by a growth of activity in the ethylene dibromide and tri- and tetrabromoethane fractions. This was consistent with the presence, as impurities, of vinyl and hydrogen bromide.

In view of this irreproducibility, the equality of the retentions for the different isotopes, which has been found to hold in a number of bromides, was adopted as a criterion for the

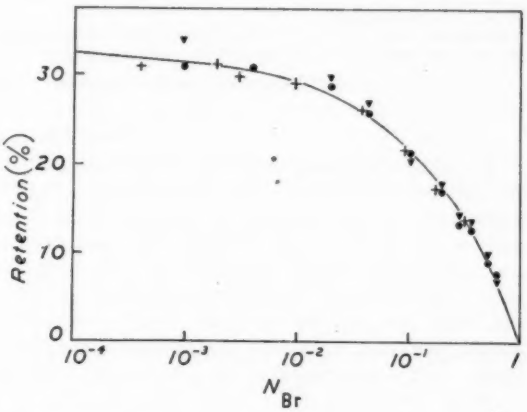

FIG. 1. *Retention of ethylene dibromide as a function of the molar fraction of bromine.*

\+ ^{80}Br, ● ^{80}Br*, ▼ ^{82}Br.

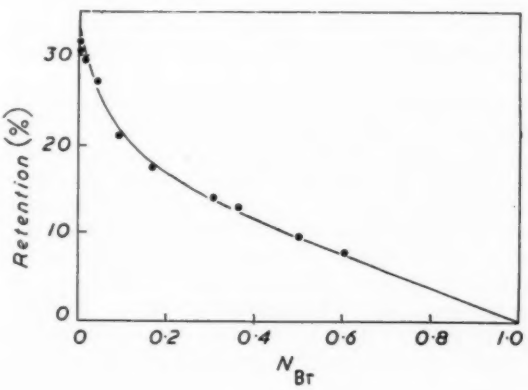

FIG. 2. *Retention of ethylene dibromide as a function of the molar fraction of bromine. The points shown are the weighted mean of the values, shown in* FIG. 1, *taken at the same molar fraction of bromine.*

acceptance of results obtained for the ^{80}Br* and ^{82}Br isotopes. It can be seen from Fig. 1 that the retentions of all isotopes are equal for large bromine concentrations; at low concentrations some values for ^{82}Br lie considerably higher than those corresponding for ^{80}Br*; these were included since the equality of the latter with those obtained for ^{80}Br indicated the general validity of the lower group of points. The curves drawn in Figs. 1 and 2 will be discussed later.[14]

The products from neutron irradiation are given in Table 2, the results shown being obtained from the weighted mean of the activities found for ^{80}Br* and ^{82}Br; for a given fraction, the latter were equal within the errors of counting.

[14] Milman and Shaw, *J.*, 1957, 1325.

TABLE 2.

	Percentage activity in fraction shown : (*a*) N_{Br} = 10^{-3}	(*b*) N_{Br} = 0·312	(*c*) % activity in (*a*) / % activity in (*b*)	(*d*) Activity at $N_{Br} = 0$ due to (i) High-energy processes	(ii) Diffusive processes
Methylene dibromide ...	2·05 ± 0·11	1·27 ± 0·07	1·61 ± 0·13	1·84 ± 0·10	0·21 ± 0·15
Ethylidene dibromide ...	1·51 ± 0·08	0·89 ± 0·03	1·70 ± 0·06	1·29 ± 0·04	0·21 ± 0·09
Ethylene dibromide.....	15·81 ± 0·43	5·89 ± 0·07	2·69 ± 0·08	8·50 ± 0·10	7·31 ± 0·44
Bromoform	2·05 ± 0·11	1·21 ± 0·11	1·70 ± 0·18	1·75 ± 0·16	0·30 ± 0·19
1 : 1 : 2-Tribromoethane	5·18 ± 0·16	2·85 ± 0·05	1·82 ± 0·06	4·00 ± 0·07 2·36 ± 0·06 *	1·18 ± 0·18 2·82 ± 0·17 *
1 : 1 : 2 : 2-Tetrabromoethane (residue)	1·47 ± 0·13	0·95 ± 0·04	1·45 ± 0·14	1·38 ± 0·06	0·09 ± 0·14
Observed retention	30·42 ± 0·75	14·08 ± 0·18	—	—	—

* Calculated from the results of Table 1, experiment (*e*).

DISCUSSION

By using the extrapolation method described previously [1] the value of R_E (retention due to high-energy processes) obtained from Fig. 2 is approximately 18%. A similar linear form for the variation of R_E with molar fraction of bromine being assumed, the ratio of R_E at N_{Br} 0 and 0·312 is 1·45, and the corresponding ratios of the percentage activities of any fraction produced by high-energy processes might be expected to be the same. The observed ratios for the individual fractions are given in Table 2, column (*c*), and, with the possible exception of the tetrabromoethane fraction, the ratios are all greater than this, indicating that diffusive processes are partly responsible for their formation. If it is assumed that the active compounds produced when 0·312 molar fraction of bromine was present are entirely due to high-energy processes, the corresponding values at zero bromine concentration can be obtained, and hence also the degree to which diffusive reactions contribute to the different products. The results are given in Table 2, (*d*), from which it can be seen that the predominant diffusive reactions result in the formation of ethylene dibromide and tribromoethane.

The greater value of R_E for ethylene dibromide than for ethyl bromide suggests that Br–Br collisions play an important part in the high-energy processes, possibly by their ability to " thermalise " energetic atoms in a single encounter,[4] so that the active atom is surrounded by the radicals previously produced by inelastic collisions. In the absence of such collisions a slower degradation of the energy associated with the active atom might occur, so that when the atom was finally thermal there would be a smaller concentration of nieghbouring free radicals, and hence a smaller chance of recombination. The greater concentration of (bound) bromine atoms in ethylene dibromide than in ethyl bromide might therefore be expected to give an increased yield of high-energy products. Evidence for the occurrence of processes of the type postulated by Libby [4] may also be afforded by the greater yield of parent compound produced by high-energy processes (8·5%) than with that found in ethyl bromide (6·1%).

In the presence of small quantities of bromine the percentage of tribromoethane is often greater than that found in the pure substance [compare, for example, Table 1, (*e*) with Table 2, (*a*)]. This implies that the reactions producing this substance involve the addition of elementary bromine to active vinyl bromide. Also, the " diffusive " dependence of the tribromoethane fraction on bromine concentration suggests that part of the active vinyl bromide is formed at this stage, the most probable mechanism for this being by exchange of inactive vinyl bromide (formed by high-energy processes) with active atoms. The observed reduction in activity of the tribromoethane when the bromine concentration is increased can then be explained by the removal of inactive vinyl bromide by addition, or, more probably, of active atoms by the reaction :

$$Br^* + Br_2 \longrightarrow Br + BrBr^*$$

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The ethylene dibromide activities found in the pure system were greater than those obtained when bromine was present and are consistent with the view that the homogeneous reactions

$$CH_2{:}CHBr + HBr^* \longrightarrow CH_2Br{\cdot}CH_2Br^* \longleftarrow CH_2{:}CHBr^* + HBr$$

partly account for the activity in this fraction. The rôle of bromine, when present, is most probably to saturate vinyl bromide produced on storage or by radiolysis, thus preventing such reactions. Further evidence for the formation of ethylene dibromide by slow reactions (in the absence of bromine) is given by the greater percentage activity of ^{82}Br (than of $^{80}Br^*$) in this fraction since, by virtue of its greater half-life, molecules of vinyl or hydrogen bromide containing ^{82}Br are available for such reactions for longer than similar molecules containing $^{80}Br^*$. Similar effects are observed for the tri- and tetra-bromoethane (residue) fractions, both of which are partly derived from vinyl bromide.

The erratic variation of retention with the time of irradiation [cf. Table 1, (*c*), (*d*), (*e*), (*f*)] can be explained if the purification of specimens (*c*) and (*d*) were more effective in removing hydrogen bromide than vinyl bromide. The large initial activity of vinyl bromide would then be expected; subsequent formation of vinyl bromide by radiolysis would be accompanied by the liberation of hydrogen bromide, and the latter might reduce the rate of formation of vinyl bromide by the competing exchange :

$$HBr + Br^* \longrightarrow HBr^* + Br$$

For experiments (*e*) and (*f*), in which there was a much smaller initial vinyl bromide concentration, the simultaneous formation of vinyl and hydrogen bromide could cause an increased vinyl bromide fraction.

A further observation, in empirical agreement with the above arguments, is the smaller percentage of active vinyl bromide containing ^{82}Br rather than $^{80}Br^*$; this can be seen in experiments (*a*), (*d*), and (*f*) (Table 1) and has also been found in three other analyses (unpublished). Such an effect would be expected if the rate of removal of active vinyl bromide by addition reactions was greater than its rate of production by the reactions described, or by slow γ-ray induced exchange with extractable radio-bromine. Evidence for such exchange in ethyl bromide containing 1 : 2-dibromoethylene is given later.[15] If precautions are taken to avoid such reactions, the retention of ethylene dibromide in the presence of 1 : 2-dibromoethylene is about 50%,[15] and the retentions in ethyl bromide containing either this substance or vinyl bromide are equal. In these conditions, the maximum retention expected in ethylene dibromide in the presence of vinyl bromide is therefore 50% also; the greater retentions found (Table 1) therefore indicate that γ-ray induced exchange might also contribute to the formation of active vinyl bromide.

The bromoform activities in Table 1 show a similar difference in the percentage activities for the two isotopes to that found in the neighbouring fractions. Since the separation of bromoform from the other carriers is difficult to perform quickly, it seemed possible that this effect was spurious and due to poor fractionation. However, this was disproved by comparing the ratio (% activity as ^{82}Br/% activity as $^{80}Br^*$) for the ethylene dibromide, bromoform, and tribromoethane fractions from the results of twelve analyses; in four cases the observed ratio for bromoform was significantly greater than that for the corresponding neighbouring fraction, showing that the increased ^{82}Br activity cannot always be ascribed to poor separation. It may be observed empirically that large activities in the bromoform fraction are generally accompanied by large residual activities. Since the latter are probably due to compounds derived from polymerised vinyl bromide, this suggests that the activity collected with the bromoform fraction might be due to other chemical species produced by addition of free radicals to vinyl bromide.

Another puzzling feature of the analyses is the similarity between the vinyl bromide and the methylene and ethylidene dibromide fractions, all of which tend to give smaller activities for the longer-lived isotope. This suggests the presence of an impurity (*e.g.*,

[15] Milman and Shaw, following paper.

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1 : 2-dibromoethylene) which reacts similarly to vinyl bromide and boils between 100° and 110°. However, the complexity of the slow processes occurring in bromine-free ethylene dibromide can be largely explained by the formation of vinyl bromide, and no attempt was made to investigate the latter surmise.

Experimental

Materials.—Ethylene bromide was obtained from The Associated Ethyl Company; samples were kept in daylight with excess of bromine for 2 hr., then extracted with sulphite, washed with water, and dried ($CaCl_2$). The samples were then filtered and fractionally distilled as described for ethyl bromide.[1] Specimens were then stored in the dark until required. Preliminary experiments showed that this purification did not give more irreproducible results than specimens purified by Willard's method; [1] in view of the similarity of the results obtained with ethyl bromide purified by the two methods, the former was always used. Vinyl bromide was made from ethylene dibromide by refluxing the latter with alcoholic potassium hydroxide. A Drikold trap at the top of the reflux condenser collected most of the vinyl bromide, which was purified by fractional distillation in a vacuum-jacketed column cooled externally with melting ice. The fraction, b. p. 15·5—16°, was collected and sealed in small glass ampoules which were kept in darkness until needed. Specimens left in daylight formed white crystals which were assumed to be polymer.

Bromine (" AnalaR ") was used without further purification.

Technique.—The neutron irradiation, and methods of extracting and counting ethylene dibromide, were exactly as described for ethyl bromide.

In order to check that no exchange occurred between ethylene dibromide and hydrogen bromide, a mixture of them was prepared by passing hydrogen bromide from pile-produced $NH_4{}^{82}Br$ into ethylene dibromide, as described by Milman and Shaw,[9] the only modification being that traces of bromine were removed by bubbling the hydrogen bromide through ethylene dibromide instead of bromobenzene. The sample was placed near the radium–beryllium source for eight days, and then extracted. A period of two days was allowed before measurement to reduce the activity of $^{80}Br^*$ produced from the source. The corresponding ^{82}Br activity was negligible compared with that from the $H^{82}Br$ introduced. If it is assumed that the activity in the extracted fraction was produced by exchange, the rate found corresponded to a fraction exchanging per hour of 7×10^{-4}.

The products from neutron irradiation were analysed by extracting about 37 ml. of a 50 ml. irradiated specimen. The unextracted portion was used to determine the total activity; 12 ml. of the rest were used to determine the retention which was corrected [1] for any activity adhering to the walls of the irradiation flask. After being dried ($CaCl_2$), 25 ml. were mixed with 10 ml. each of all carriers except vinyl bromide, and the mixture was re-extracted to ensure the removal of bromine. After being dried ($CaCl_2$), the mixture was cooled in Drikold, and 10 ml. of pre-cooled vinyl bromide was added. After filtration, the mixture was fractionally distilled,[1] the column and collecting vessel being cooled initially in melting ice. The vinyl bromide recovered was diluted to 50 ml. with pre-cooled carbon tetrachloride; other samples were prepared for measurement as described previously.[15]

In addition to the purification described above, a little of the ethylene dibromide was boiled off at atmospheric pressure in samples (*a*), (*b*), (*c*), and (*d*) (Table 1) to remove most of the vinyl and hydrogen bromide which might have been formed during storage. Samples (*e*) and (*f*) were purified before irradiation by cooling a stoppered flask containing ethylene dibromide in an ice-bath; when about three quarters had frozen, the liquid was poured off in a dry-box and the solid was allowed to melt. The process, which was performed in diffuse light, was repeated twice, the product from the final melt being used.

The retention of ^{80}Br in ethyl bromide containing vinyl bromide (10^{-3} molar fraction) was measured by irradiating the mixture for 10 min. and extracting with a bromide–sulphite reagent.

Attempts to produce ethylene dibromide enriched in vinyl bromide by boiling were made by refluxing it in a glass system. The exit tube from the reflux condenser was held under more ethylene dibromide contained in a bubbler, the outlet of which was attached to a tube containing sodium hydroxide pellets to remove any hydrogen bromide evolved and to prevent ingress of moisture. After 20 days, the ethylene dibromide from the boiling flask and the bubbler were mixed and distilled, the first ml. being collected in a freshly purified ethylene dibromide sample.

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This, together with another sample from the same batch, was irradiated overnight, and the retentions were measured. The analysis was performed after the extracted solution had been treated with bromine to saturate vinyl bromide present; the latter was not added as carrier in this case.

By keeping aliquot portions of the same specimen of ethylene dibromide in darkness, daylight, and near a 500 mc Ra source production of hydrogen bromide was found to be greatest for the specimen held in daylight and least for that kept in the dark. These results might indicate the relative dissociation of ethylene dibromide under such conditions. The results obtained by adding bromine labelled with ^{82}Br (prepared as described previously [2]) to these samples were inconclusive, but activity was always found in the ethylene dibromide and the tri- and tetra-bromoethane (residue) fraction. The latter was further distilled at 1·5 cm. admixed with pentyl benzoate, benzyl benzoate, 1 : 3 : 5-tribromobenzene, and dibutyl phthalate to provide higher-boiling carrier material. The residual activity was approximately equally distributed between tetrabromoethane and higher-boiling compounds. Of the latter, it was estimated that 10% boiled above 300° (at atmospheric pressure), the activity per unit temperature range between 260° and 300° being roughly constant.

Retentions in Bromine–Ethylene Dibromide Mixtures.—These and the analysis of the products were determined as described for ethyl bromide.[1]

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THE CLARENDON LABORATORY, OXFORD. [*Received, July 19th*, 1956.]

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251. *The Nature of the Diffusion-controlled Reactions following Neutron Capture in Alkyl Bromides.*

By MIRIAM MILMAN and P. F. D. SHAW.

The variation of retention caused by adding 1 : 2-dibromoethylene to ethyl bromide, ethylene and ethylidene dibromide, and 1 : 1 : 2-tri- and 1 : 1 : 2 : 2-tetra-bromoethane has been investigated in an attempt to elucidate the nature of diffusion-controlled reactions undergone by radicals resulting from neutron capture in these bromides. It is concluded that a large proportion of the radio-bromine atoms, which diffuse from the site of neutron capture, is probably produced by reaction of organic radicals with HBr* and Br_2* formed by high-energy processes.

A MAJOR difficulty in the quantitative treatment of the diffusive reactions following neutron capture in organic halides is the lack of knowledge of their chemical nature. It has been shown [1,2] that, in ethyl bromide and ethylene dibromide, the radioactive products from such reactions are relatively simple, consisting chiefly of the parent compound. If the latter are produced predominantly (in diffusive processes) by combination of the active atoms with free radicals, other reactions removing radicals will also be important, since the extent to which they occur will partly determine the number of radicals available for reaction with the active atom. These reactions cannot be completely determined because, in some cases, no radio-bromine will be involved, and the quantities of the inactive products are too small for conventional analysis; however, it was expected that some evidence for their nature might be found by studying the variation of R_D and A (defined below) as a function of the relative number of hydrogen and bromine atoms in the parent compound.

In this and the following paper, A is defined as the fraction of the total radio-bromine produced which diffuses from the second (diffusion-dependent) stage, and which reacts with small quantities ($\sim 10^{-4}$ molar fraction) of 1 : 2-dibromoethylene present in the

[1] Milman and Shaw, *J.*, 1957, 1308.
[2] Milman, Shaw, and Simpson, preceding paper.

irradiated bromide; R_E and R_D are, respectively, the retentions produced by the high-energy and diffusion-dependent processes and refer to the pure (bromine-free) liquid.

Goldhaber and Willard,[3] and Roy, Williams, and Hamill [4] interpreted the rise in retention, from 32% to 60%, caused by 1 : 2-dibromoethylene to mean that A is 28% and that the remaining inorganic activity (40%) is present as molecules formed by the high-energy processes. They do not appear to have considered the possibility that reactions such as

$$R + BrBr^* \longrightarrow RBr^* + Br \quad . . . . . (a)$$

$$R + BrBr^* \longrightarrow RBr + Br^* \quad . . . . . (b)$$

or

$$R + HBr \longrightarrow RH + Br^* \quad . . . . . (c)$$

(where R = Et) might also be important in the diffusive stage. If this were so, the yield of inorganic molecules from high-energy processes would be greater than that estimated.[3,4]

Reactions (*a*), (*b*), and (*c*), where R = Et or C_2H_4Br, require little or no activation energy,[5,6,7] and it will be assumed that they are equally probable, given a suitable collision, to recombination of radicals (or atoms).

To simplify discussion, let us temporarily neglect the possibility that an active bromine atom, produced by high-energy reactions, may escape diffusive reaction, and also the possible occurrence of the diffusive reactions

$$R + Br^* \longrightarrow RBr^* \quad . . . . . (d)$$

$$Br + Br^* \longrightarrow BrBr^* \quad . . . . . (e)$$

$$H + Br^* \longrightarrow HBr^* \quad . . . . . (f)$$

In these conditions the only active bromine atoms produced are those from reactions (*b*) and (*c*), and the diffusive yield of the parent compound will be from reaction (*a*). A will therefore be determined by (*b*) and (*c*), and R_D by (*a*), which is as probable as (*b*). The quantity $(A - R_D)$ should therefore be a measure of the amount of HBr^* produced in the high-energy processes, and this should decrease as the ratio of hydrogen to bromine atoms decreases in the parent compound.

The possibility of reactions (*d*), (*e*), and (*f*) must now be considered. If (*d*) is important in the diffusion-dependent reactions (as has been postulated [3,4]) it would be expected that (*e*) and (*f*) might also be important, since it is improbable that in a single recoil the radio-bromine is the only atom produced. Small quantities of 1 : 2-dibromoethylene (10^{-4}—10^{-3} molar fraction) are unlikely to affect the course of the reactions occurring in the diffusive stage, the observed increase in retention being due to exchange with radio-bromine atoms which were produced either in the high-energy or the diffusive process, and which escape further reactions [such as (*d*), (*e*), or (*f*)]. If the latter reactions were important in the diffusive stage, greater concentration of 1 : 2-dibromoethylene should lead to the interception and exchange of radio-bromine atoms by the reaction :

$$CHBr{:}CHBr + Br^* \longrightarrow CHBr{:}CHBr^* + Br$$

so that radio-bromine atoms which previously formed inorganic molecules by (*e*) or (*f*) would be returned to organic combination. The curve of retention against molar fraction of 1 : 2-dibromoethylene might then be expected to show a sharp initial increase in retention in the same way that addition of bromine to the pure bromide causes the retention to fall rapidly.

This argument presupposes that, for suitable collisions, the probability of exchange by reaction (*d*) is comparable with that for recombination by (*c*). This is supported by the formation in ethylene dibromide of tribromoethane by diffusive reactions,[2] and indicates

[3] Goldhaber and Willard, *J. Amer. Chem. Soc.*, 1952, **74**, 318.
[4] Roy, Williams, and Hamill, *ibid.*, 1954, **76**, 3274.
[5] Sherman, Quimby, and Sutherland, *J. Chem. Phys.*, 1936, **4**, 732.
[6] Muller and Schumacher, *Z. phys. Chem.*, 1939, *B*, **42**, 327.
[7] Anderson and Van Artsdalen, *J. Chem. Phys.*, 1944, **12**, 479.

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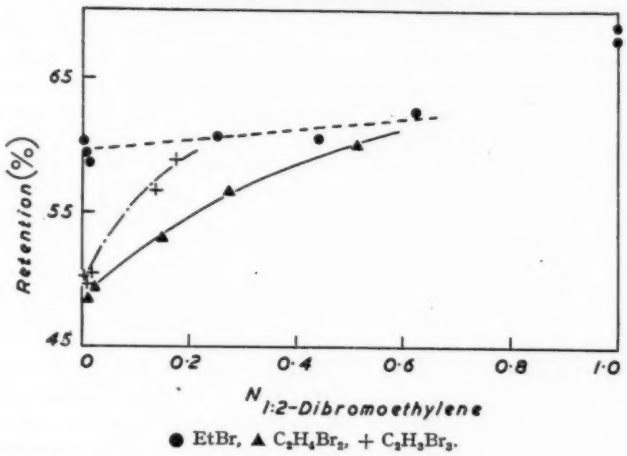
that vinyl bromide, which reacts similarly to 1 : 2-dibromoethylene, can compete with atoms or free radicals for the active atom.

Part of the object of this work was therefore to investigate the nature of the diffusion-dependent reactions following neutron capture.

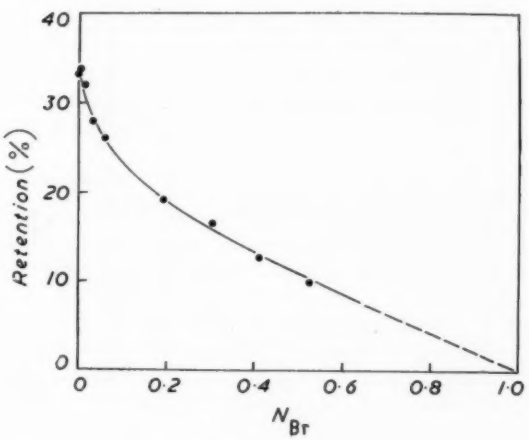
The molecular products from the high-energy reactions must be affected by the probability that, when the active atom is thermal, a high density of radicals or atoms is

FIG. 1. *Retention of ethyl bromide, ethylene dibromide, and tribromoethane as a function of the molar fraction of* 1 : 2*-dibromoethylene.*



● EtBr, ▲ $C_2H_4Br_2$, + $C_2H_3Br_3$.

FIG. 2. *Retention of ethylidene dibromide as a function of the molar fraction of bromine.*



available for combination with it. This high density is most probable immediately after the passage of a highly energetic atom, since they will recombine rapidly, and consequently the yield of high-energy products must depend on the efficiency of retardation of an energetic atom to thermal velocities. Since a single Br–Br collision (regarded as elastic) can reduce the energy of a recoiling atom to the thermal region, the yield of active molecules from the high-energy processes should increase with the density of bromine atoms in the bromide irradiated. Such an effect has been found in ethyl bromide and ethylene

dibromide,[1,2] and the work now described was undertaken partly to see whether this was a general feature of Szilard–Chalmers reactions.

Effect of 1 : 2-*Dibromoethylene.*—Preliminary experiments with short irradiation times and measurement of the retentions of ^{80}Br (half-life, 18 min.) confirmed results obtained with ethyl bromide,[3,4] but the retentions for $^{80}Br^{*}$ (half-life, 4·4 hr.), obtained after longer irradiation periods, were anomalously large, especially if the bromo-olefin was carefully purified. This suggested that a more general exchange occurred, probably induced by γ-radiation from the neutron source. This was confirmed by analysis of a

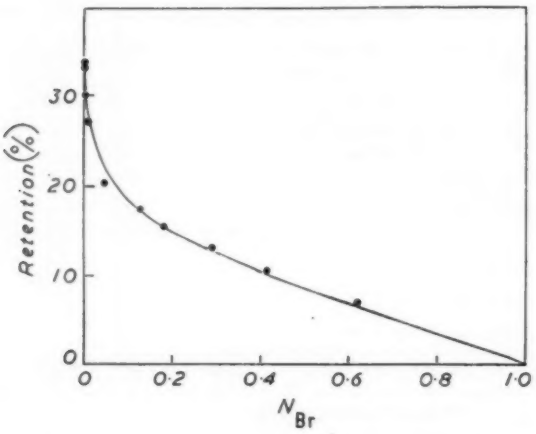


FIG. 3. *Retention of tribromoethane as a function of the molar fraction of bromine.*

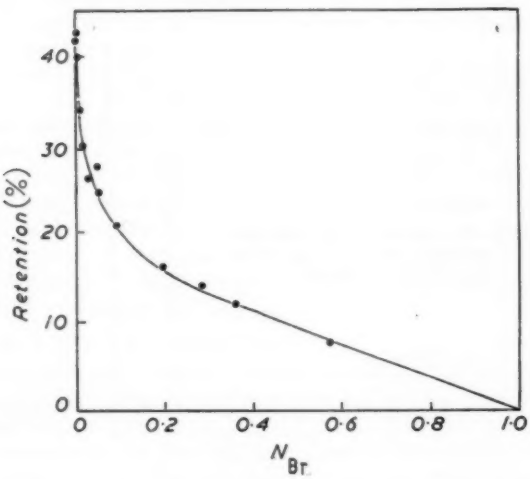


FIG. 4. *Retention of tetrabromoethane as a function of the molar fraction of bromine.*

specimen which contained 10^{-3} molar fraction of 1 : 2-dibromoethylene and gave a high retention (81%), the activity present as 1 : 2-dibromoethylene being 51%. If a little nitrogen dioxide (approximately 10^{-3} molar fraction of NO_2) was dissolved in the olefin, the γ-ray induced exchange was inhibited, probably by the breaking of a self-propagating chain reaction (cf. Milman and Shaw [8]) but the non-homogeneous exchange, involving active atoms diffusing from the sites of neutron capture, still took place and reproducible

[8] Milman and Shaw, *J.*, 1956, 2101.

retentions of 60% were obtained. Under these conditions prolonged irradiation still caused high retentions, and in order to complete the experiment within the induction period caused by the inhibitor, the irradiation-times were kept small (10 min.) and the retentions of ^{80}Br were measured. The results obtained for ethyl bromide, ethylene dibromide, and 1 : 1 : 2-tribromoethane are shown in Fig. 1. The retentions observed when small quantities ($\sim 10^{-3}$ molar fraction) of 1 : 2-dibromoethylene were present in ethylidene dibromide and 1 : 1 : 2 : 2-tetrabromoethane were 50 ± 1 and $57 \pm 2\%$ respectively.

Retentions with Bromine Present.—These for ethylidene dibromide and tri- and tetrabromoethane are shown as a function of the molar fraction of bromine present in Figs. 2, 3, and 4. They were measured by using short irradiation times and by counting the ^{80}Br produced. This ensured that the effect of slow addition reactions, of the type found in ethylene dibromide, was not important, even when the bromine concentration was small.

The high energy retentions can be obtained [3,4] by extrapolation of the curves found for large molar fractions (N) of bromine. Since R_D should be a continuous function of bromine concentration, the observed retentions should reach the straight line joining R_E (at $N_{Br} = 0$) to zero (at $N_{Br} = 1$) asymptotically; consequently it is difficult to estimate the best line for the extrapolation since the best line through the experimental points will tend to include a small contribution due to diffusive retention. Hence, the values for R_E in the Table are slightly lower than those which would have been obtained by direct extrapolation through the experimental points, the magnitude of the reduction being based empirically on the curve-fitting to be described.[9] Values of R_E for ethyl bromide and ethylene dibromide are also included in the Table; their slight reduction from the values previously given [1,2] does not affect the arguments previously based on them.

In view of the difficulty experienced with ethylene dibromide [2] no attempt was made to obtain the retention in the bromine-free bromides, except in the case of ethyl bromide. Values of the retention at zero bromine concentration were obtained by extrapolation from those found when small quantities of bromine were present; this is justified by the equality of the retentions found in ethyl bromide directly, and by using this technique. The retentions produced by diffusive reactions (R_D) are given in the Table, and were obtained by subtraction of R_E from the total retention (R). The percentage of radio-bromine escaping as atoms (A) was found by subtraction of R from the retention obtained in the presence of small quantities of 1 : 2-dibromoethylene.

Discussion

The Table shows that the increase of R_E for ethyl bromide and ethylene dibromide is not sustained when the number of bromine atoms per molecule is further increased; consequently, if arguments such as those advanced by Libby [10] or on p. 1319 are relevant to the high-energy processes, some sort of "saturation effect" occurs. If the concentration of bromine atoms (taken independently of their state of combination) is low, as in ethyl bromide, the energy lost by collision with atoms other than bromine may be of

	Ethyl bromide	Ethylene dibromide	Ethylidene dibromide	1 : 1 : 2-Tribromoethane	1 : 1 : 2 : 2-Tetrabromoethane
R (%)	32	33	34	35	42
R_E (%)	14	17	19	17	18
R_D (%)	18	16	15	18	24
A (%)	27·5	16	16	15	15
$(A - R_D)$	9·5	0	1	−3	−9
P_E	0·39	0·50	0·48	0·54	0·61

comparable importance in the slowing-down process. Since such collisions can only produce "thermal" atoms relatively slowly, considerable recombination of the radicals

[9] Milman and Shaw, following paper.
[10] Libby, *J. Amer. Chem. Soc.*, 1947, **69**, 2523.

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produced might occur before a reaction such as (*d*) is possible. The free-radical concentration immediately surrounding the thermalised atom might therefore be less for ethyl bromide than for ethylene dibromide, and therefore a smaller value of R_E might be expected in the former. If the efficiency of thermalisation increases sharply with the concentration of (bound) bromine atoms, a state of " saturation " can be envisaged where nearly all the recoil atoms are slowed down so rapidly that, when thermal, they are initially surrounded only by atoms and molecular fragments. Under these conditions, R_E will be determined solely by the relative number of atoms or radicals competing for the active atom. Since the organic products from the high-energy processes in ethyl bromide and ethylene dibromide [1,2] consist predominantly of the parent compound or its singly substituted derivatives, it might be expected that in all bromides roughly equal numbers of atoms and radicals would surround the active atom, so that R_E would be roughly constant under " saturation " conditions. The relatively low values of R_E can be explained by assuming that steric effects are more important in the combination of the active atom with an organic radical than with another (hydrogen or bromine) atom. In consequence, the yield of high-energy active products should consist predominantly of molecules rather than atoms, though the latter might result if the surrounding radicals and atoms combined with each other, leaving the active bromine atom surrounded by the newly formed molecules.

The lack of a sharp initial rise in the curve of retention against molar fraction of 1 : 2-dibromoethylene in ethyl bromide (Fig. 1) indicates that reactions (*e*) and (*f*) [and also, by implication, (*d*)] are not important in the diffusive stage. Since active atoms are known to be produced by the high-energy *and* diffusion-dependent reactions, this strongly suggests that the diffusive reactions (*b*) and (*c*) are responsible for the production of free active atoms, and that the active inorganic high-energy products consist predominantly of molecules rather than atoms.

If it is temporarily assumed that A measures the total number of active bromine atoms produced by reactions (*b*) and (*c*), and R_D measures the RBr* molecules from reaction (*a*), the quantity $(A - R_D)$ should be related to the amount of HBr* produced by high-energy reactions, and should decrease as the number of hydrogen atoms per molecule of the irradiated bromide is reduced. The Table shows that this effect was found, although the negative values for tri- and tetra-bromoethane cannot be explained without further assumption, since, on the above premises, R_D cannot exceed A because of the equal probabilities of reactions (*a*) and (*b*). If the efficiency of thermalisation is increased as the number of (bound) bromine atoms in the parent substance increases, the products from the high-energy reactions would be confined to a smaller volume of liquid near the site of neutron capture. Under such conditions the diffusive reactions might become more complex, first leading to the formation of bromine atoms from the high-energy molecular products by reactions (*a*), (*b*), and (*c*); if this happened before the radicals which had not reacted had been greatly dispersed by diffusion, reactions (*d*), (*e*), and (*f*) could then occur so that R_D would increase at the expense of A, the quantity $(A - R_D)$ becoming negative. Conversely, in a relatively more disperse system of radicals, etc., the probability of the active bromine atom's being involved in two consecutive reactions in the diffusive stage will be considerably decreased.

The shapes of the curves (Fig. 1) for ethylene dibromide and tribromoethane are in qualitative agreement with this argument, for they indicate that the atomic recombinations (*e*) and (*f*) occur in the diffusion-dependent processes. Further, the initial slope (for low molar fractions of 1 : 2-dibromoethylene) of the curve for tribromoethane is greater than that for ethylene dibromide, showing that the recombination reactions become more important as the number of bromine atoms per molecule of the parent compound is increased.

The interpretation of the processes following neutron capture given above is reasonably consistent with the data obtained, and will be used as a basis for the treatment of the diffusive reactions which is attempted in the following paper.

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For this, it is desirable to estimate the probability that collision between an organic radical and the inorganic species containing radio-bromine will lead to the formation of an organic radio-bromine compound. Such probabilities depend on the relative amounts of hydrogen bromide and bromine present, and therefore on the irradiated halide; also, they might be expected to vary when the overall density of bromine atoms is altered by addition of elementary bromine to a given bromide. Adopting the above arguments, we see that reactions (*a*), (*b*), (*c*), and (*d*) produce either an organic radio-bromide or a radio-bromine atom. If we assume that, given a suitable collision, the probabilities of these reactions are equal, the extent to which such reactions occur is proportional, approximately, to $(A + R_D)$; the fraction of such collisions leading to organic retention is therefore approximately $R_D/(A + R_D)$. Values of this quantity (P_R) are listed in the Table, and are given approximately by the empirical relation

$$P_R = 0{\cdot}30 + [0{\cdot}92 \times 10^{-3} \times \text{(Molecular weight of irradiated substance)}]$$

Several features, however, are not explained by the above arguments, which suggest that R_D should increase with the number of bromine atoms per molecule; for example, if the slowing-down is more efficient in a medium containing a high density of bromine atoms, the initial radical concentration should be greater, so that diffusive reactions become more important. It can be seen from the Table that in moving from ethyl bromide to ethylene dibromide R_D decreases, and then increases steadily for the remaining bromides. This could be explained if ethyl radicals were more stable than bromoethyl and similar radicals, which may dissociate into a bromine atom and an olefin molecule before the termination of the diffusive processes. The activation energy for such dissociation for the bromoethyl group has been reported [5] as 13 ± 2 kcal./mole, whereas for the dissociation into ethylene and a hydrogen atom the ethyl radical would require at least 45 kcal./mole, the endothermicity of the reaction (calculated from bond energies given by Pauling [11]).

An alternative explanation is that the probability of reaction with bromine, etc., is less for a bromoethyl than for an ethyl radical. This could arise by stabilisation due to the greater electron density available from the bromine atoms in bromoethyl radicals. Sherman *et al.*[5] have calculated that the activation energy of the reaction

$$CH_2Br{\cdot}CH_2 + Br_2 \longrightarrow CH_2Br{\cdot}CH_2Br + Br$$

is 2·3 kcal./mole; experimentally, Muller and Schumacher [6] found this to be greater than 5 kcal./mole, but the other results [7, 12] are consistent with the assumption that the similar reactions involving methyl or ethyl radicals have zero, or a very small, activation energy.

A further point requiring explanation is the difference in R_E found for ethylene and ethylidene dibromides. On the model used for the high-energy processes (*i.e.*, where inelastic processes are important, but the effectiveness of atoms in slowing the recoiling atom is based on Libby's " billiard-ball " hypothesis) equality of R_E might have been expected, since the constituent atoms are the same in each case. The difference therefore illustrates the inadequacy of such a treatment, which was chosen primarily for its simplicity. However, it is possible that the explanation of the difference in R_E is that different steric effects operate in the combination of the thermalised atom with the surrounding molecular fragments.

An alternative explanation of the more effective thermalisation, postulated in bromides containing more than one bromine atom, can be based on the degree of inelasticity of the collisions. For example, as the mass of the molecules increases, it might be expected that the walls of the cage holding a molecule hit by a recoiling atom would become more " rigid " owing to the greater inertia of the surrounding molecules. Consequently, more energy could be transferred to the molecular bonds in heavily brominated compounds than in ethyl bromide, so that the recoil energy should be dissipated more rapidly and within a

[11] Pauling, " The Nature of the Chemical Bond," Cornell Univ. Press, 1940, 2nd Edn.
[12] Kistiakowsky and Van Artsdalen, *J. Chem. Phys.*, 1944, **12**, 469.

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smaller volume; also, the products from the high-energy reactions should indicate greater fragmentation of the parent molecules. Possible evidence for the latter might be given by the sum of the methylene dibromide and bromoform activities found in ethylene dibromide [2] (4·1%) which is greater than the corresponding quantity for ethyl bromide [1] (2·8%). On this basis, differences in R_E for substances containing different arrangements of the same atoms might arise from the ability of the molecules to group themselves in formations corresponding to greater or less " rigidity " in the wall of the liquid cage.

Summarising the conclusions of this and the preceding papers,[1,2] we obtain the following picture of the processes following neutron capture :

(i) The recoil atom moves through the liquid, losing its energy by inelastic processes until it is finally thermal. The local concentration of free radicals, molecular fragments, and atoms existing after the passage of the recoil atom is extremely high, so that an immediate recombination occurs in which most of the radicals, etc., will form stable molecules. Owing to the random nature of such recombination, some radicals will be isolated from each other, and thus remain to react in the subsequent diffusive stage. The more highly fragmented molecules thus isolated must disproportionate, or react with solvent molecules to form ethyl or bromoethyl radicals, since there is little evidence for their existence in the subsequent diffusive reactions. After the termination of the high-energy reactions, the radio-bromine atom will be either in organic combination (contributing to R_E) or otherwise present predominantly as HBr* or BrBr*. It seems improbable that the amount remaining as atomic bromine is as large as thought previously.[3,4]

(ii) The radicals resulting from (i) diffuse from the sites of their formation and react with inorganic compounds produced in (i) or recombine mutually. Reaction with Br*Br or Br* gives molecules of the parent substance contributing to R_D. It appears that a considerable fraction of the atomic radio-bromine present at the end of this stage results from diffusive, rather than high-energy, reactions. In ethylene dibromide, and probably also in compounds containing more bromine atoms per molecule, exchange reactions between radio-bromine atoms and vinyl bromides [produced in stage (i)] may also contribute to the diffusive retention.

These reactions proceed until the concentrations of the reactants are so reduced by diffusion that their reaction probability is insignificant. Radio-bromine atoms which escape reaction ultimately form inorganic compounds, probably by reactions of the type : [4]

$$EtBr + Br^* \longrightarrow C_2H_4Br\cdot + HBr$$

Experimental

Organic bromides were obtained from British Drug Houses Ltd., and, except for 1 : 2-dibromoethylene, all were distilled and then kept with bromine in daylight for a few hours. The bromine was then removed by sulphite extraction; the bromide was dried ($CaCl_2$) and fractionally distilled in a dark room with a column (40 × 1·5 cm.) packed with glass helices; a middle fraction was retained. The 1 : 2-dibromoethylene was fractionally distilled in darkness without pre-treatment; " AnalaR " bromine was used without further purification.

Experiments with 1 : 2-*Dibromoethylene.*—Known volumes of the organic bromide and 1 : 2-dibromoethylene were mixed in diffuse light, and were irradiated as already described.[1] Extractions were made with bromide–sulphite solutions in diffuse light to reduce the possibility of light-induced exchange or addition reactions between the extractable radio-bromine and 1 : 2-dibromoethylene. The retentions in ethylidene dibromide and tri- and tetra-bromoethane, and mixtures containing a large proportion of 1 : 2-dibromoethylene were measured by using 5 ml. irradiated specimens. The total activity was measured after dilution of 2 ml. of these with 10 ml. of carbon tetrachloride; 2 ml. were extracted and similarly diluted before separation from the aqueous layer. Counts and precautions were as previously described.[1]

Preliminary experiments with ethyl bromide containing a little 1 : 2-dibromoethylene showed that overnight irradiations gave higher retentions for $^{80}Br^*$ than short (4 hr.) irradiations. Organic products were analysed by adding carriers, including 1 : 2-dibromoethylene, to an extracted portion of a specimen giving high retention (81%) and separating them by

fractional distillation; methylene and ethylidene dibromide and 1 : 2-dibromoethylene were collected together, the activity of this mixed fraction being 55% of the total. After allowance for the expected activity of methylene and ethylidene dibromide (4% [1]) the activity of 1 : 2-dibromoethylene (51%) corresponds closely to the rise in retention (81 − 32 = 49%) caused by addition of this substance, thus showing that exchange reactions are responsible for the anomalously high retention observed.

The behaviour of ethyl bromide–1 : 2-dibromoethylene mixtures was erratic when the molar fraction of the latter was large, high retentions being sometimes observed even for short irradiation times. When this occurred, traces of bromine added to the mixture in daylight disappeared rapidly, there being no noticeable induction period. Experiment showed that nitrous fumes dissolved in the olefin caused an induction period, and the use of such mixtures gave consistent results providing that the irradiation times were short; these were therefore restricted to 10 min., and measurements were confined to ^{80}Br. Air was not excluded, so that the inhibiting agent was probably nitrogen dioxide, the concentration of which was found by shaking the olefin with dilute sodium hydroxide and separating. Dissolved olefin was removed by four extractions with carbon tetrachloride and the aqueous layer was acidified and titrated with 0·01N-potassium permanganate.

The solution of nitrogen dioxide in 1 : 2-dibromoethylene was always checked before use by ascertaining that the retention of ethyl bromide containing a trace (10^{-4}—10^{-3} molar fraction) of the bromo-olefin gave a retention of about 60%.

Retentions with Bromine Present.—These were measured as described previously; [1] the activities were corrected for solution density and the volume of bromine present. Retentions in ethylidene dibromide and tri- and tetra-bromoethane were determined for 5 ml. samples by using the dilution technique described above.

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252. *The Non-homogeneous Reactions following Neutron Capture in Organic Bromides.*

By MIRIAM MILMAN and P. F. D. SHAW.

An attempt is made to treat quantitatively the kinetics of the reactions occurring between radicals and inorganic radio-bromine compounds formed near the site of neutron capture. Allowance for the dilution of the reactants by diffusion has been made by considering these to be held uniformly in a sphere of liquid whose radius increases with time. By making reasonable assumptions regarding the rates of the reactions involved, curves have been obtained which fit the experimentally determined variation of retention with bromine concentration in ethyl bromide, ethylene dibromide, and tri- and tetra-bromoethane.

THE sharp fall in retention which is observed when small quantities of elementary bromine are added to organic bromides before neutron irradiation has been ascribed [1,2] to thermal processes involving diffusion of the radicals produced by the recoil atom. The preceding papers [3,4,5] support this view, and also provide evidence for the nature of such diffusive reactions.

The basic difficulty in a quantitative treatment of the kinetics of such reactions, where some of the reactants are not homogeneously distributed, is to allow for diffusion. The general equation describing such processes is

$$dc/dt = D\nabla^2 c - k_c c^2 - k_s cs \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (i)$$

[1] Goldhaber and Willard, *J. Amer. Chem. Soc.*, 1952, **74**, 318.
[2] Roy, Williams, and Hamill, *ibid.*, 1954, **76**, 3274.
[3] Milman and Shaw, *J.*, 1957, 1303.
[4] Milman, Shaw, and Simpson, *J.*, 1957, 1310.
[5] *Idem*, preceding paper.

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The first term takes account of the diffusion (coefficient = D), the second the recombination between radicals at concentration c, and the third represents reaction between the radicals and some other species (concentration s) which may be uniformly dispersed throughout the system.

Approximations have been made to make this equation solvable. Of these, most assume that the radical distribution is Gaussian, and remains so with time (cf., *e.g.*, Krenz [6]); in particular this assumption is inherent in the treatment by Samuel and Magee [7] which has been applied by Roy *et al.*[2] to the recombination occurring in Szilard–Chalmers reactions.

This assumption makes the mathematical handling of the equation easier; this is its only justification. There are two possible criticisms of such a treatment applied to recoil effects. The initial Gaussian distribution is expected if a cluster of non-reactive radicals started from a point and were allowed to diffuse freely through the liquid. Such distributions only hold for a large number of diffusive " jumps " (displacement from one " lattice " site in the liquid to a neighbouring one), and in the present case this approximation may not be valid. For example, if it is assumed that the mean energy of a bromine atom following neutron capture is 50 ev and that Br–Br (elastic) collisions are chiefly responsible for its slowing down, the mean time for the energy to become about 1 ev must be approximately that required to make 7 suitable collisions, since the mean fraction of the energy lost per collision is 0·5. If x is the mean distance between bromine atoms, and v_0 the initial recoil velocity, the time required to make these is $(x/v_0)\{1 + (2)^{\frac{1}{2}} + (2) + \ldots . (2)^{6/2}\}$, *i.e.*, about $25x/v_0$. Any potential barrier to diffusion being neglected, the mean time for a thermal atom to traverse x is x/v; since v_0 is 45 times greater than v it can be seen that the recoil atom is thermalised in a time which is small compared with that required for thermal atoms or radicals to move one molecular diameter. This argument is extremely crude, and neglects the increased rates of diffusion of the radicals which would be expected in view of the large energies involved, but it indicates that any large amount of diffusion such as that necessary to obtain an initial Gaussian distribution is unlikely.

The second criticism of the treatments cited is that if recombination is to be important, the concentration distribution cannot remain Gaussian since the rate of recombination is proportional to c^2 and therefore the central maximum of the latter will be depressed more rapidly with time than its periphery. Also, if the diffusive reactions are imagined to occurr after the high-energy recombinations, it seems improbable that the initial distribution of radicals will be Gaussian.

An alternative assumption which enables us to solve eqn. (i) is that the radicals produced are held at uniform concentration in a small sphere of liquid, the periphery of which expands at a rate given by the mean distance traversed in a three-dimensional random walk. A similar picture of the diffusive reactions occurring near more energetic particle tracks has been given by Magee.[8] The initial distribution of the radicals produced by recoil atoms may be reasonably well interpreted by this assumption, since the energetic atom will be widely scattered so that an approximately spherical radical distribution might result.

In a random-walk treatment, the mean displacement (r), in time t, of radicals starting from a point and diffusing in all directions is given by :

$$r^2 = (1/3)\delta^2\nu t = 2Dt \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(ii)}$$

where ν is the frequency at which steps of length δ (assumed subsequently to be a molecular diameter) are taken and D is the diffusion coefficient. At any time (t) after neutron capture, the volume containing the radicals, etc., is given by :

$$V(t) = (4/3)\pi[2D(t_0 + t)]^{3/2}]$$

[6] Krenz, *J. Chim. phys.*, 1951, **48**, 237.
[7] Samuel and Magee, *J. Chem. Phys.*, 1953, **21**, 1080.
[8] Magee, *J. Chim. phys.*, 1955, **52**, 528.

where t_0 is a constant which determines the initial size of the radical cluster. The rate of combination of a group of radicals diffusing from a common origin is given by

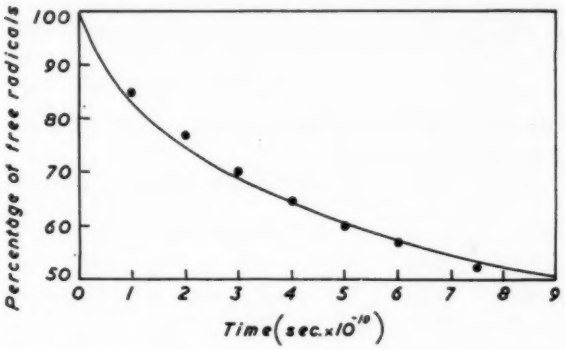
$$-\mathrm{d}n(t)/\mathrm{d}t = k[n(t)]^2/[\rho V(t)] = k[n(t)]^2/[\alpha(t_0 + t)^{3/2}]$$

where $$\alpha = 4\pi(2D)^{3/2}\rho/3$$

or $$1/n(t) - 1/n(0) = 2(k/\alpha)\{t_0^{-\frac{1}{2}} - (t_0 + t)^{-\frac{1}{2}}\} \quad . \quad . \quad . \quad . \quad . \quad \text{(iii)}$$

where $n(t)$ is the number of radicals present at time t, ρ is the number of solvent molecules in unit volume, and k is a reaction constant equal to a collision number multiplied by the probability of recombination per collision.

This treatment of the diffusion is unrealistic, and it is of interest to compare it with some other in which it is possible to treat the diffusion more realistically. This has been performed for a radical distribution which was initially Gaussian, by calculating the recombination occurring in individual shell-like volumes round the origin. The decrease



The percentage of free radicals as a function of time. The curve is for a Gaussian distribution. The points were obtained from the simple theory by adjustment of t_0.

in the number of radicals was found for a period of 10^{-10} sec. and the new radical concentration in each shell was calculated. The number of radicals diffusing from one shell into its neighbour in the same time was then found from the formula

$$\Delta n/\Delta t = DA(\partial c/\partial r)$$

where Δn is the decrease in the number of radicals enclosed in a shell having surface area A in a time Δt (10^{-10} sec.). $(\partial c/\partial r)$ is the concentration gradient determined from the slope of a constructed curve. The number of radicals reacting in the next 10^{-10} sec. interval was then determined and the process repeated several times. The curve of the number of radicals which had reacted in time t is given in the Figure and was obtained from the initial Gaussian distribution

$$c_r = c_0/\lambda^3(2\pi)^{3/2} \exp[-(r^2/2\lambda^2)]$$

where c_r is the concentration at a distance r from the origin.

The following values of the constants required for the construction of the curve in the Figure were chosen arbitrarily; $c_0 = 19{\cdot}3$; $\lambda = 8{\cdot}75 \times 10^{-8}$ cm.; $k = 1{\cdot}63 \times 10^{10}$/sec.; $D = 1{\cdot}16 \times 10^{-5}$ cm.^{2}/sec., and $\rho = 7{\cdot}15 \times 10^{21}$/cm.^{3}. The points shown were obtained from (iii) by using the same values of k, ρ, and D. It can be seen that, by suitable adjustment of t_0, the simplified treatment can be made to give a satisfactory description of such diffusive processes; the value of t_0 chosen was $15{\cdot}2 \times 10^{-10}$ sec. and corresponds to an initial radius of the radical cluster of 18·7 Å, a value just greater than twice the Gaussian modulus (λ).

Application to Szilard–Chalmers Reactions.—In order to apply the above treatment to Szilard–Chalmers reactions, it is convenient to take initially a simplified view of the

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diffusive processes. In the presence of bromine (where c now represents the molar fraction N_{Br}) the rate of disappearance of organic radicals [number $n_1(t)$] from the system at time t is given by

$$-\frac{dn_1(t)}{dt} = \frac{k[n_1(t)]^2}{\alpha(t_0+t)^{3/2}} + k_2 n_1(t)c + \frac{k_3 n_1(t) n_2(t)}{\alpha(t_0+t)^{3/2}} \quad . \quad . \quad . \quad . \quad \text{(iv)}$$

where k_1, k_2, and k_3 are reaction constants governing recombination, reaction with (inactive) bromine, and combination with the active bromine atom respectively. $n_2(t)$ is the number of radio-bromine atoms in the " reaction " volume at time t; strictly its value can only be unity for a single recoil, and therefore it must be regarded as the mean fraction (obtained from the average of many recoil events) of such atoms existing at time t. Temporarily, let us regard the radio-bromine atom as being free, allowance being made subsequently for the possibility of its being present as molecular bromine or hydrogen bromide; further, we shall also suppose that $n_1(t) > n_2(t)$, so that the last term of (iv) can be neglected in comparison with the first, and that c remains unaltered despite the large free-radical concentration produced in the vicinity of the recoil atom.

The rate of reaction of the radio-bromine atoms to give organic retention is

$$-dn_2(t)/dt = k_3 n_1(t) n_2(t)/[\alpha(t_0+t)^{3/2}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(v)}$$

The solution of these equations, which was obtained by Professor M. H. L. Pryce, is given in the Appendix and is :

$$n_2(\infty)/n_2(0) = [1 + x(1-y)]^{-k_3/k_1} \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(vi)}$$

where

$$x = 2k_1 n_1(0)/(\alpha t_0^{\frac{1}{2}}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(vii)}$$

and

$$y = \pi^{\frac{1}{2}}(k_2 c t_0)^{\frac{1}{2}} e^{k_2 c t_0} \left[1 - (2/\sqrt{\pi}) \int_0^{\sqrt{(k_2 c t_0)}} e^{-z^2} dz\right] \quad . \quad . \quad . \quad . \quad . \quad \text{(viii)}$$

The quantity $n_2(\infty)/n_2(0)$ represents the fraction of radio-bromine atoms which escapes reaction with other radicals, and therefore the quantity $[1 - n_2(\infty)/n_2(0)]$ is the fraction of the atoms which has undergone diffusive retention.

If n_2 is now re-defined to mean the number of inorganic molecules (or atoms) of any type containing the radio-bromine atom, the fraction of the collisions between these and the organic radicals which is successful in causing organic retention of the radio-bromine will be P_R (preceding paper) so that the overall diffusive retention $[R_D(c)]$ becomes $P_R[1 - n_2(\infty)/n_2(0)]$. Strictly, it may be more rigorous to multiply the right-hand term of (v) by P_R, and the introduction of P_R after finding $[n_2(\infty)/n_2(0)]$ is only justified by the greater ease of curve-fitting which results from this treatment. However, neither treatment will be exact, if, as seems probable, the distribution of the active chemical species undergoing reaction alters with time, so that P_R should be a function of time rather than the mean value used.

The value of P_R obviously depends on the bromine concentration since, when this is large, it must influence the ultimate form of the radio-bromine atom resulting from the high-energy processes. For example, it would be expected that, as the bromine concentration becomes greater, more BrBr* might be produced at the expense of HBr*. Since it is not possible to determine the value of P_R directly in such circumstances it is assumed that the expression $P_R = 0{\cdot}30 + 0{\cdot}92 \times 10^{-3}M$ holds,[5] where M is the effective molecular weight [equal to $c \times$ (molecular weight of bromine) + $(1 - c) \times$ (molecular weight of RBr)].

A further correction must also be introduced, since the above values of P_R were determined for pure organic bromides. Since the number of solvent molecules affected by the recoil will be reduced when c is increased, the number of resulting organic free radicals

will be less, and hence also the total number of collisions leading to retention of the radio-bromine. To allow for this, the value of $R_D(c)$ obtained above has been multiplied by $(1 - c)$, the molar fraction of the organic bromide.

Finally, the value of $R_D(c)$ must be normalised to take account of the retention due to high-energy processes. The value of the latter is $R_E(1 - c)$, since it is known empirically [3, 4] to be a linear function of c; the fraction of the total radio-bromine available to undergo diffusive reactions is therefore $[1 - R_E(1 - c)]$.

The complete expression for $R_D(c)$ is therefore

$$R_D(c) = [1 - R_E(1 - c)](1 - c)P_R[1 - n_2(\infty)/n_2(0)] \quad . \quad . \quad . \quad \text{(ix)}$$

and that for the total retention, $R(c)$:

$$R(c) = R_E(1 - c) + R_D(c) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(x)}$$

The curves drawn for the retention as a function of the molar fraction of bromine in the preceding papers were given by (x) by making the assumption that $k_3 = k_1$. The values of R_E and P_R are given in the preceding paper, the x and k_2t_0 values shown in the Table also being used. Curves of reasonable fit can also be obtained by using modified values of the ratio k_3/k_1; values of x and k_2t_0 giving reasonable agreement with the experimental data are also given in the Table for $k_3/k_1 = 0{\cdot}5$.

	Ethyl bromide		Ethylene dibromide		Tribromoethane		Tetrabromoethane	
	(*a*)	(*b*)	(*a*)	(*b*)	(*a*)	(*b*)	(*a*)	(*b*)
x	1·10	3·40	0·62	1·62	0·74	1·96	0·90	2·60
k_2t_0	23·4	34·0	8·7	11·2	34·1	39·5	36·0	41·8
10^5D (cm.^{2}/sec.)	3·0		0·67		0·32		0·15	
$10^8\delta$ (cm.)	6·2		6·5		6·9		7·2	
$10^{-10}\nu$	4·66		0·95		0·40		0·17	
$10^{10}t_0f_2$	5·0	7·3	9·15	11·7	86·1	98·5	212	246
$10^8r_0f_2^{\frac{1}{3}}$	17·3	21·0	11·1	12·6	23·4	25·2	25·2	27·2
10^8r_0 (cm.)	—	—	40·2	45·6	—	—	28·6	30·8
$n_1(0)f_1f_2^{\frac{1}{3}}$	4·05	15·1	1·32	4·05	3·36	9·55	4·31	13·5
$n_1(0)$	—	—	4·8	14·8	—	—	4·95	15·3

(*a*) for $k_3/k_1 = 1$. (*b*) for $k_3/k_1 = 0{\cdot}5$.

Interpretation of the constants given is very difficult in view of the uncertainty of the relative reaction rates (k_1, k_2, k_3) and the appropriate diffusion coefficients. Values of the latter have been given by Miller [9] for iodine in ethylene dibromide and tetrabromoethane, and are included in the Table. The value of D for ethyl bromide was estimated from the viscosity by assuming Stokes's law, and that for tribromoethane was found by interpolation between the values for the other bromides. Since the values of both x and k_2t_0 contain reaction constants, it is necessary to evaluate these before estimates of t_0 (and hence the initial size of the radical cluster) and $n_1(0)$ can be made. Let k_1, k_2, and k_3 equal νf_1, νf_2, and νf_3 respectively, where ν is the frequency of " lattice jumps " or collision sets in the liquid, and f is the reaction probability per collision set. ν can be estimated from the Einstein relation [10] $D = 1/6\nu\delta^2$ where δ is the mean displacement per " jump." By taking δ to be one molecular diameter, the values of ν given in the Table are obtained.

From the values of (k_2t_0) and ν, t_0f_2 may be found and hence also $r_0f_2^{\frac{1}{3}}$ [from (ii)]. If f_2 is a constant for all the bromides, it can be seen from the Table that the decrease of r_0 expected for the more heavily brominated compounds does not occur. This anomaly is removed by more careful consideration of f_2; the probability of reaction in a given collision set is of the form :

$$f = A_R \exp(-E_R/\boldsymbol{RT})/[A_R \exp(-E_R/\boldsymbol{RT}) + A_D \exp(-E_D/\boldsymbol{RT})]$$

where E_R and E_D are the activation energies required for reaction and diffusion respectively and A_R and A_D are the factors depending on the collision rate of the radical with the walls

[9] Miller, *Proc. Roy. Soc.*, 1924, *A*, **106**, 724.
[10] Einstein, *Ann. Physik*, 1905, **17**, 549.

of the liquid cage, etc.[11] E_D can be evaluated for ethylene dibromide and tetrabromoethane from Miller's data [9] by assuming that the dependence of D on temperature is of the form $D = D_0 \exp(-E_D/RT)$ (cf. Frenkel [12]). The values of E_D obtained for these substances are 3·5 and 5·7 kcal./mole respectively.

E_R for the reaction :

$$BrCH_2{\cdot}CH_2{\cdot} + Br_2 \longrightarrow BrCH_2{\cdot}CH_2Br + Br \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (a)$$

is greater [14] than 5 kcal./mole; by taking the lowest estimate of E_R, and by assuming the equality of A_R and A_D, the values of f_2 for ethylene dibromide and tetrabromoethane are 0·076 and 0·77 respectively. The values of r_0 obtained are shown in the Table, and exhibit the expected fall in moving to tetrabromoethane. Similar calculations for ethyl bromide and tribromoethane are prevented by the lack of diffusion data; however, it is reasonable to suppose that E_D increases in the series of bromides, in which case the value of r_0 for ethyl bromide might be anomalously high. This could be accounted for if the activation energy of the reaction :

$$C_2H_5{\cdot} + Br_2 \longrightarrow C_2H_5Br + Br{\cdot} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (b)$$

is lower than that of reaction (*a*). This seems probable when the data of Anderson and Van Artsdalen [13] are compared with those of Muller and Schumacher.[14]

The values of r_0 are subject to large uncertainty in view of the assumptions which are necessarily made. For ethyl bromide, the distance moved by a recoil atom should correspond to about six molecular diameters (an average of 1 Br–Br collision per molecule being assumed), *i.e.*, the value of r_0 expected should be *ca.* 18 Å. For the more heavily brominated compounds this should be less. However, enhanced diffusion owing to the effective rise in temperature of the molecules near the recoil site, or delay of a γ-ray in the cascade following neutron capture would both cause a wider spread of the radicals before recombination by diffusion could occur, and in view of this the values of r_0 do not seem unreasonable.

The remaining factor of interest is $n_1(0)$, the number of radicals initially present in the " reaction volume." This can be calculated in terms of f_1 and f_2 from (vii) by using the t_0 values already determined. It can be seen that the values of $n_1(0)f_1f_2^{\frac{1}{2}}$ given in the Table are sensitive to changes in the value of k_3/k_1 chosen. By assuming the above values of f_2, and also that f_1 is unity for recombination reactions, the values of $n_1(0)$ for ethylene dibromide and tetrabromoethane can be calculated. The smallness of the $n_1(0)$ values (for k_3/k_1 unity) is consistent with the picture of the events following neutron capture given previously [5] since the bulk of the radicals produced will be removed in the " high-energy " recombination processes. A further factor which might also account for this is that inactive bromine or hydrogen bromide molecules, produced by the recoil, will reduce the local free-radical concentration by reactions other than the simple recombination postulated. Since no transfer of activity results from such processes, it is not possible to estimate their importance, but it might be expected that, owing to this effect, the effective number of radicals would be less than the true number present. The $n_1(0)$ values also reflect the uncertainty in f_2; comparison of the values of $n_1(0)f_1f_2^{\frac{1}{2}}$ indicates that if the value of f_2 used for ethylene dibromide were also applied to ethyl bromide, $n_1(0)$ for the latter would be 14·5, a value considerably greater than that found for ethylene dibromide or tetrabromoethane. However, if it is assumed [12] that reaction (*b*) has zero activation energy, this anomaly is removed.

The treatment given might help to account for the equality, in a given bromide, of the retentions of the different bromine isotopes. *A priori*, these might be expected to differ, since the γ-ray cascades following neutron capture, and hence the mean recoil energies, might differ considerably for the three isotopes produced. At zero bromine concentration

[11] Williamson and LaMer, *J. Amer. Chem. Soc.*, 1948, **70**, 717.
[12] Frenkel, " Kinetic Theory of Liquids," Clarendon Press, 1946, p. 190.
[13] Anderson and Van Artsdalen, *J. Chem. Phys.*, 1944, **12**, 479.
[14] Muller and Schumacher, *Z. phys. Chem.*, 1939, *B*, **42**, 327.

R_D is determined solely by x, y being zero; for a given bromide, x is proportional to $n_1(0)/t_0^{\frac{1}{2}}$ which corresponds to the number of radicals produced per unit length of recoil track. If the latter were constant over the range of recoil energies produced by neutron capture, values of R_D for the isotopes would be expected to be equal.

The constancy of R_E for the different isotopes cannot yet be explained in view of the lack of data concerning the γ-ray cascades following neutron capture by the bromine isotopes, and the uncertainty of the exact nature of the high-energy processes. However, it is possible to formulate the simplest assumptions, based on the conclusions of the preceding paper, which could lead to constant isotopic R_E values.

To account for the approximate constancy of R_E (obtained for any isotope) in bromides containing more than one bromine atom per molecule, it has been postulated that the high-energy products result from a system in which the thermalised atom is surrounded by a cluster of free radicals and atoms, the ratio of the numbers of these being constant. For such a state to be probable, an atom having an energy E_0 (the minimum energy to ensure the complete dissociation of the neighbouring molecules) must be rapidly degraded to thermal energies. Such thermalisation must occur without appreciable diffusion of the active atom; consequently it must be brought about by inelastic collisions rather than elastic processes involving several collisions. It therefore seems probable that the process of "inelastic" thermalisation is the same as that producing the dissociation of the surrounding molecules.

The constancy of R_E for the different isotopes can be explained if it is further assumed that the majority of the individual recoil energies for any of the bromine isotopes is greater than E_0, and also that the slowing by inelastic collisions is roughly continuous, so that a stage where the energy is reduced to E_0 is probable for all atoms. It is improbable that the value of E_0 would be less than 15 ev, but a proper estimate cannot be made owing to the lack of a theoretical basis for the inelastic slowing-down process; this need, of course, makes the whole explanation of the constancy of R_E extremely tentative.

It is interesting to compare the present results for the diffusive retentions in ethyl bromide with those obtained by Roy *et al.*[2] who have also attempted a treatment of the non-homogeneous reactions following neutron capture. These authors concluded that, in ethyl bromide, the latter could be well represented by the combination of a single radical with the active atom, the distance between these being of the order of a molecular diameter. In the present treatment, the value of $n_1(0)/r_0$ required to give a retention of 32% at zero bromine concentration is $2{\cdot}33 \times 10^7$; if it is assumed that only one radical is involved and that f_1, f_2, and f_3 are unity, this corresponds to an initial recoil volume of radius 4·3 Å. However, this initial condition is not consistent with the $(k_2 t_0)$ term necessary to give the correct shape to the curve of retention against bromine concentration, unless a higher value of k_2 than that estimated in the present work is adopted.

The semi-empirical treatment of the diffusive processes given above accounts for most of the known features of Szilard–Chalmers reactions. Although the treatment of such reactions is naïve, and justified only by the convenience of its solution, a more realistic approach does not seem to be yet warranted in view of the uncertainty of several details of the process. In particular, reactions between radicals and other inactive species can only be inferred, and their real importance cannot be properly estimated; also, the relative importance of reactions involving the radio-bromine atom cannot be properly assessed, because knowledge of their activation energies is either lacking or too imprecise.

Appendix

The equations to be solved are (iv) and (v).

By integration of (iv) (omitting the last term) between the limits $t = 0$ and T,

$$\frac{1}{n_1(T)} = \exp(k_2 cT)\left[\frac{1}{n_1(0)} + \frac{k_1}{\alpha}\int_0^T \frac{\exp(-k_2 cs)}{(t_0+s)^{3/2}}\,\mathrm{d}s\right] \quad . \quad . \quad . \quad . \quad \text{(xi)}$$

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By integration of (v) between the limits $t = 0$ and ∞,

$$n_2(\infty) = n_2(0) \exp\left[-\frac{k_3}{\alpha}\int_0^\infty \frac{n_1(t)\,dt}{(t_0+t)^{3/2}}\right] \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(xii)}$$

By rearrangement of (iv) :

$$\frac{k_1 n_1(t)\,dt}{\alpha(t_0+t)^{3/2}} = -\left[k_2 c + \frac{1}{n_1(t)}\frac{dn_1(t)}{dt}\right]dt \quad . \quad . \quad . \quad . \quad . \quad \text{(xiii)}$$

Integrating :

$$\frac{k_1}{\alpha}\int_0^\infty \frac{n_1(t)\,dt}{(t_0+t)^{3/2}} = \underset{T\to\infty}{\text{Lim.}} -\left[[k_2 cT + \ln\frac{n_1(T)}{n_1(0)}\right] = \underset{T\to\infty}{\text{Lim.}} \ln\frac{n_1(0)}{n_1(T)}\exp(-k_2 cT)$$

$$= \ln\left[1 + \frac{k_1 n_1(0)}{\alpha}\int_0^\infty \frac{\exp(-k_2 cs)}{(t_0+s)^{3/2}}\,ds\right] \quad . \quad . \quad . \quad . \quad \text{(xiv)}$$

by substitution from (xi).

From (xii) and (xiv),

$$\ln\left(\frac{n_2(\infty)}{n_2(0)}\right) = -\frac{k_3}{k_1}\ln\left[1 + \frac{k_1 n_1(0)}{\alpha}\int_0^\infty \frac{\exp(-k_2 cs)}{(t_0+s)^{3/2}}\,ds\right]$$

or

$$\frac{n_2(\infty)}{n_2(0)} = \left[1 + \frac{k_1 n_1(0)}{\alpha}\int_0^\infty \frac{\exp(-k_2 cs)}{(t_0+s)^{3/2}}\,ds\right]^{-k_3/k_1} \quad . \quad . \quad . \quad . \quad \text{(xv)}$$

The solution of the remaining integral is straightforward, and is :

$$\int_0^\infty \frac{\exp(-k_2 cs)}{(t_0+s)^{3/2}}\,ds = \frac{2}{t_0^{\frac{1}{2}}}\left\{1 - \sqrt{\pi}(k_2 ct_0)^{\frac{1}{2}}\exp(k_2 ct_0)\left[1 - \frac{2}{\sqrt{\pi}}\int_0^{\sqrt{(k_2 ct_0)}}\exp(-z^2)dz\right]\right\}.$$

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THE CLARENDON LABORATORY, OXFORD. [*Received, July 19th,* 1956.]

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253. *Infrared Spectra of Natural Products. Part VII.* The Identification and Location of Ethylenic Double Bonds in Pentacyclic Triterpenoids.*

By A. R. H. COLE and D. W. THORNTON.

Frequencies and peak intensities of infrared bands in the regions of C=C stretching, C–H stretching, and C–H bending absorption are given for a number of different locations of ethylenic double bonds (both isolated and conjugated) in compounds based on oleanane, ursane, and lupane. Differences in ring strain account for differences in C=C stretching frequencies compared with those for comparable positions in steroids. The use of " adjacent methylene " absorption near 1435 cm.$^{-1}$ in the detection of tetrasubstituted double bonds is described.

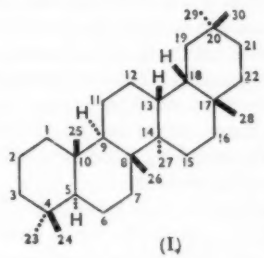
THREE types of infrared absorption band are commonly investigated for the identification and location of ethylenic double bonds in organic compounds,[1-3] *viz.*, that due to the C=C

* Part VI, *J.*, 1956, 4868.

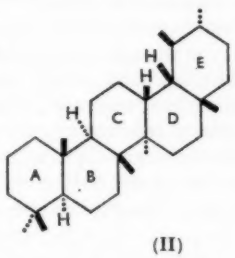
[1] Bellamy, " The Infrared Spectra of Complex Molecules," Methuen, London, 1954.
[2] Jones, Humphries, Packard, and Dobriner, *J. Amer. Chem. Soc.*, 1950, **72**, 86.
[3] Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402; Henbest, Meakins, and Wood, *J.*, 1954, 800.

stretching vibration (1580—1680 cm.$^{-1}$) and the bands in the regions of stretching (3000—3080 cm.$^{-1}$) and bending (680—1000 cm.$^{-1}$) vibrations of the C–H bonds attached to the trigonal carbon atoms. A fourth type of band, due to a bending vibration of methylene groups adjacent to double bonds, has been identified in work on steroids.[4] The present work is part of an investigation of the relations between the structures of triterpenoids and their infrared spectra.[5]

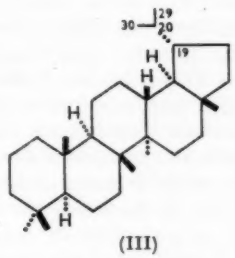
The compounds described here are based on the hydrocarbons oleanane (I), ursane (II), and lupane (III) and contain double bonds in a variety of positions, mostly isolated but occasionally conjugated with other ethylenic bonds or carbonyl groups. While the structures of oleanane and lupane have been completely established, controversy exists over the structure of the ursane–α-amyrin series,[6] but the numbering and location of the double bonds in these compounds is unambiguous.[7, 8]



(I)



(II)



(III)

(*A*) *Non-conjugated Double Bonds.*—(1) C=C *Stretching absorption.* Since the C=C system is relatively non-polar the absorption due to its stretching vibration is very weak, and its detection by single-beam spectroscopy is made difficult by the water-vapour absorption of the atmosphere. If the air in the spectrometer is dried and a background spectrum is recorded on each chart, quite weak bands can be found, but double-beam instruments are preferred for work in this region.

The double-bond stretching frequencies of the individual compounds are given in Table 1 and characteristic frequencies for the different structures are summarised in Table 3. Representative compounds have been studied quantitatively so that in work on new substances the required concentration of solution for a given cell length can be readily calculated. The peak intensity is of the order of 0·1—0·02 of that of a carbonyl band. Intensity values have not been given where the relevant bands occur on the side of overlapping intense carbonyl bands. The exact frequencies of the olean-18-ene compounds are not quite as certain as the others because of their low intensity. This low intensity is brought about by the presence of the *gem*-dimethyl group on $C_{(20)}$ which makes its environment much more nearly symmetrical than that of double bonds in most other positions. A few compounds were studied in chloroform solution, but there is virtually no shift in C=C absorption frequency in this solvent compared with that in carbon tetrachloride.

The stretching frequencies of the isolated endocyclic double bonds studied here do not vary significantly from one another, indicating that they are subject to approximately equal amounts of ring-strain. The data are useful for indicating the presence of trisubstituted ethylenic systems, but, apart from the low intensity of the Δ^{18}-type, the C=C stretching absorption does not assist much in fixing the position of this type of double bond

[4] Jones and Cole, *J. Amer. Chem. Soc.*, 1952, **74**, 5648; Jones, Cole, and Nolin, *ibid.*, p. 5662.
[5] Cole and Thornton, *J.*, 1956, 1007.
[6] Meisels, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1949, **32**, 1075; Melera, Arigoni, Eschenmoser, Jeger, and Ruzicka, *ibid.*, 1956, **39**, 441; Beaton, Spring, Stevenson, and Strachan, *J.*, 1955, 2610; Meakins, *Chem. and Ind.*, 1955, 1353; Corey and Ursprung, *J. Amer. Chem. Soc.*, 1956, **78**, 183; Phillips and Tuites, *Chem. and Ind.*, 1956, R 29; Cole, Thornton, and White, *Chem. and Ind.*, 1956, 795.
[7] Guider, Halsall, and Jones, *J.*, 1953, 3024.
[8] *J.*, 1953, 4203.

in a new compound. The vinylidene group in the side-chain of the lupeol series can be easily identified by the relatively strong band ($\varepsilon \sim 60$) at 1640—1642 cm.$^{-1}$.

The C=C stretching frequency of the very common Δ^{12}-compounds varies over rather a wide range, the few very high results being given by compounds containing 3- and 19-carbonyl groups. While it is quite likely that the presence of a trigonal carbon atom in the E ring could influence the Δ^{12}-C=C stretching frequency, the same group at $C_{(3)}$ seems rather too remote to have any similar effect. The " normal " Δ^{12}-frequency may be taken as 1654—1657 cm.$^{-1}$, as exhibited by α- and β-amyrin and urs-12-ene.

Also it seems unlikely that the carbonyl group in methyl 3-oxo-olean-18-en-28-oate (methyl moronate, C=C 1661 cm.$^{-1}$) could be responsible for the high C=C stretching frequency compared with those of methyl morolate (1656 cm.$^{-1}$) and morene (1647 cm.$^{-1}$).

Not many of the ethylenic double bonds in the pentacyclic triterpenoids can be directly compared with corresponding positions in the steroids,[2,3,9] but it is interesting that while the Δ^{2}-C=C frequency (1653—1661 cm.$^{-1}$) is practically the same in both series, the $\Delta^{9(11)}$-type has a significantly higher frequency in the triterpenoids (1660 cm.$^{-1}$; cf. steroids 1643—1648 cm.$^{-1}$). This is related to the decrease in ring strain on increasing the size of the neighbouring D-ring from five to six members, since ring strain is known [3] to cause a lowering of endocyclic double-bond stretching frequency. The lower strain in the $\Delta^{9(11)}$-triterpenoids is also reflected in the absence of an ethylenic C–H stretching band near 3042 cm.$^{-1}$ which is easily detected in the spectra of the $\Delta^{9(11)}$-steroids (see below).

(2) =C–H *Stretching absorption.* Usually the absorption of an ethylenic C–H group appears as a shoulder or weak band on the high-frequency side of the main C–H band, which is made up of overlapping absorption bands of methyl (2872 and 2962 cm.$^{-1}$) and methylene (2853 and 2926 cm.$^{-1}$) groups. In the steroids, confirmatory information on the presence and amount of strain in most types of double bonds can readily be obtained from this region,[2,3] but the large number of methyl groups in the triterpenoids means that the absorption at 2962 cm.$^{-1}$ is greatly intensified. The overlap of this absorption often prevents detection of the ethylenic C–H absorption. In the trisubstituted systems it is, at best, only just discernible as an unresolved shoulder and often not visible.

Ring strain causes an increase in the frequency of this absorption, taking it away from the methyl absorption, and it occurs as a distinct band at 3037 cm.$^{-1}$ in the spectrum of ursa-9(11) : 12-diene [10] where the presence of two double bonds in the same ring considerably raises the strain. Conjugation of the double bonds may also contribute to this effect.

The vinylidene group in the side chain of the lupeol series has a very characteristic C–H stretching band at 3070 cm.$^{-1}$, which is raised to 3080, but lowered in intensity, when conjugated with a carbonyl group.

The spectra of the two $\Delta^{2:12}$-dienes studied have well-defined shoulders at 3000 and 3010 cm.$^{-1}$ respectively. This is most probably due to the *cis*-disubstituted Δ^{2}-system since the corresponding absorption of 2 : 3- and 6 : 7-double bonds in the steroids [9] occurs near this position and is slightly more intense than that of a trisubstituted double bond.

A similar type of absorption, near 3045 cm.$^{-1}$, found in the spectra of triterpenoids containing a CH_2 group in a 3-membered ring (*e.g.*, in phyllanthol) has been described in an earlier paper of this series.[11]

(3) =C–H *Bending absorption.* Tables 1 and 3 include the frequencies and some intensities of bands due to bending vibrations of ethylenic C–H groups. Most of the double bonds studied here are trisubstituted and give rise to one or more relatively weak bands [12] in the range 800—840 cm.$^{-1}$. It is not clear why more than one band in this

[9] For summaries, see Cole, *Rev. Pure Appl. Chem.* (*Australia*), 1954, **4**, 111; *Fortschr. Chem. org. Naturstoffe*, 1956, **13**, 1.

[10] Newton and White, unpublished results.

[11] Cole, *J.*, 1954, 3810.

[12] Thompson and Torkington, *Proc. Roy. Soc.*, 1945, *A*, **184**, 3; *Trans. Faraday Soc.*, 1945, **41**, 246; Rasmussen and Brattain, *J. Chem. Phys.*, 1947, **15**, 120; Rasmussen, Brattain, and Zucco, *ibid.*, p. 135.

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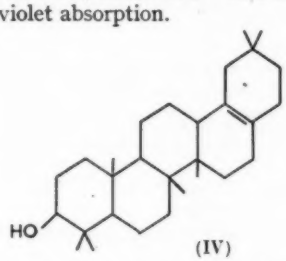
region is described as being due to a bending vibration of a lone C–H bond, but a pattern of bands is in many cases characteristic of the position of the unsaturated group in the steroid ring system.[9] The trisubstituted 12 : 13-double bonds in the triterpenoids mostly give three bands in this region, near 804, 818, and 828 cm.$^{-1}$ respectively, although occasionally the second of these is missing. The absorption of the Δ^{18}-compounds is rather erratic, while conjugation of the 12 : 13-double bond with a carbonyl group results in usually only two bands (~806, ~828). The 9(11)-double bond produces only one band, of slightly greater intensity than the other types. The C–H bending frequencies given in the summary in Table 3 have been selected to give an indication of the pattern of absorption but cannot be taken as characteristic of all compounds.

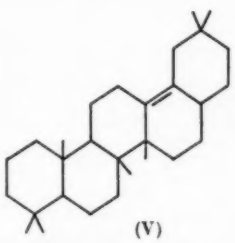
The out-of-plane C–H bending vibration of the vinylidene group of the lupeol side chain causes intense absorption at 882—885 cm.$^{-1}$ and this is the most characteristic frequency of this group (cf. 1640 and 3070 cm.$^{-1}$ above).

The *cis*-disubstituted 2:3-double bond is characterised[3] by absorption near 700 cm.$^{-1}$, due to an out-of-plane C–H bending vibration.

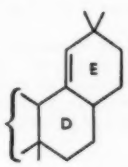
(4) *Fully substituted double bonds and adjacent methylene absorption.* When an ethylenic double bond is fully and symmetrically substituted, as in oleanol (IV), its high symmetry means that the C=C stretching vibration is inactive and the absence of ethylenic C–H bonds prevents the appearance of the characteristic C–H stretching or bending absorption bands. Its detection by infrared spectroscopy is therefore quite difficult, although Bladon, Henbest, and Wood [13] and Halsall [14] have pointed out that it can be detected by its ultraviolet absorption.



(IV)



(V)



(VI)

Jones and Cole [4,9] have shown that in the steroids this and other types of double bond cause a lowering of the bending frequency of adjacent methylene vibrations from 1450 cm.$^{-1}$ to near 1435 cm.$^{-1}$, and similar absorption is found in the spectra of unsaturated triterpenoids (Table 2). Thus, oleanol (IV) absorbs at 1437 cm.$^{-1}$ and 28-norolean-13(18)-ene (V) at 1435 cm.$^{-1}$. While this absorption will not distinguish between the two types of tetrasubstituted double bond, it does, at least, show that the unsaturated groups are present. Methyl ester groups, methylene groups adjacent to trisubstituted double bonds (Table 2), and those adjacent to some types of carbonyl groups [4,5] also absorb near 1435 cm.$^{-1}$ and these must be taken into account when looking for symmetrically substituted double bonds.

Compounds in the oleanane series, containing an 18 : 19-double bond (VI), have no adjacent methylene group and have no band near 1435 cm.$^{-1}$ (Table 2), and oxidation of Δ^{12}-compounds to the corresponding Δ^{12}-$C_{(11)}$-ketones is, of course, accompanied by a disappearance of this band.

It has been reported [15] that an in-plane deformation vibration of the $=CH_2$ system gives rise to a band at 1410—1420 cm.$^{-1}$, but no such absorption has been found in the spectra of the lupeol derivatives studied here.

(*B*) *Conjugated Dienes.*—Conjugation of double bonds leads to a lowering of frequency of the C=C stretching absorption (Table 1*B*) and frequently causes a splitting into two

[13] Bladon, Henbest, and Wood, *Chem. and Ind.*, 1951, 866.
[14] Halsall, *ibid.*, p. 867.
[15] For summary, see ref. 1, p. 46.

TABLE 1. *Frequencies (cm.$^{-1}$) with some peak intensities (in parentheses) of bands characteristic of ethylenic double bonds in pentacyclic triterpenoids.*

A blank space in this or subsequent tables means that the region has not been investigated, a dash that no absorption peak is present.

Compound	C=C stretching (CCl_4 or $CHCl_3$)	C–H stretching (CCl_4)	C–H bending (CS_2)		
(A) Non-conjugated double bonds.					
Δ^{12}-Compounds.					
Me 3 : 19-dioxo-olean-12-en-28-oate	1667	—			
Urs-12-en-3-one	1666		806(30)	—	828(30)
Me 3-oxours-12-en-28-oate	1665	3030(sh) *			
Me 3β-acetoxy-18-*iso*olean-12-en-28-oate	1663				
Me 3β-hydroxyolean-12-en-28-oate (oleanolate)	1661(15)		802(15)	816(30)	826(30)
Ursa-2 : 12-diene	1660	3000(sh)			
Me 3β-acetoxyurs-12-en-28-oate	1659	—			
Me ursa-2 : 12-dien-28-oate	1659	3010(sh)			
3β-Acetoxyolean-12-en-28-oyl chloride	1658		802(22)	816(48)	827(41)
Me 3β-acetoxyolean-12-en-28-oate	1658	—			
Me 3β-hydroxyurs-12-en-28-oate (ursolate)	1657	—	807(30)	819(19)	829(30)
Me urs-12-en-28-oate	1657	—	808(35)	819(22)	828(35)
Urs-12-ene	1657(15)	3025(sh)	805(25)	—	827(35)
Urs-12-en-3β-yl benzoate	1656	3035, 3066, 3090 †			
Olean-12-en-3β-yl benzoate	1655	3035, 3066, 3090 †	802	819	828
Urs-12-en-3β-yl acetate	1655	3025(sh)	806(35)	820(20)	828(35)
Urs-12-en-3β-ol (α-amyrin)	1654(20)	—	806(30)	—	829(30)
Olean-12-en-3β-ol (β-amyrin)	1654(15)	—	—	815(30)	828(22)
Me 3β : 19α-dihydroxyolean-12-en-28-oate	1650	3030(sh)	802(35)	817(15)	828(15)
Me 3β-acetoxy-19α-hydroxyolean-12-en-28-oate	1650(18)	3023(sh)	802(30)	817(15)	831(10)
Δ^{3}-Compounds.					
Me lup-2-en-28-oate	1661(20)	3005(sh)		729	
Ursa-2 : 12-diene	1660	3000(sh)			
Me ursa-2 : 12-dien-28-oate	1659	3010(sh)			
Δ^{18}-Compounds.					
Me 3-oxo-olean-18-en-28-oate	1661	3028(sh)	—	—	840(20)
Me 3β-hydroxyolean-18-en-28-oate	1656		802(20)	—	—
Me 3β-acetoxyolean-18-en-28-oate	1656		802(10)	—	—
Me 3β-benzoyloxyolean-18-en-28-oate	1656	3030, 3065 †	802(20)	—	—
3β-Acetoxyolean-18-en-28-al	1653(8)	3030(sh)			
Olean-18-ene-3β : 28-diol diacetate	1650		—	—	—
Olean-18-ene-3β : 28-diol diformate	1649	—			
Olean-18-ene (germanicene, morene)	1647(10)	—			
Olean-18-ene-3β : 28-diol 3-acetate	1646		—	—	—
Olean-18-en-3β-yl benzoate	1645		802(30)	819(25)	—
$\Delta^{9(11)}$-Compound.					
Olean-9(11)-ene-3β : 28-diol diacetate	1660	—	—	819(40)	—
$\Delta^{20(29)}$-Compounds.					
Lup-20(29)-en-3β-ol (lupeol)	1640(60)	3073(40)		883(180)	
Lup-20(29)-en-3β-yl acetate	1640(70)	3071		883(210)	
Lup-20(29)-en-3α-ol	1641(60)	3070(45)		882	
Lup-20(29)-en-28-ol	1641(55)	3073		883(190)	
Lup-20(29)-en-3-one	1641(65)	3070(40)			
Lup-20(29)-en-3α-yl acetate	1641(58)	3070(35)		882(220)	
Lup-20(29)-ene-3β : 28-diol 3-acetate	1641(55)	3070(37)		883(200)	
Lup-20(29)-ene-3β : 28-diol diacetate	1641(65)	3071		884(210)	
Me 3β-hydroxylup-20(29)-en-28-oate (betulate)	1641	3072		885(200)	
Me 3β-acetoxylup-20(29)-en-28-oate	1641(70)	3072(36)		884(170)	
Me 3α-acetoxylup-20(29)-en-28-oate				884	
Me 3α-hydroxylup-20(29)-en-28-oate	1642	3073(40)		885(170)	
Me 3-oxolup-20(29)-en-28-oate	1642	3073(40)			
Lup-20(29)-ene-3β : 28-diol (betulin)	1642(60)	3071			

TABLE 1. (*Continued.*)

Compound	C=C stretching (CCl_4 or $CHCl_3$)	C–H stretching (CCl_4)	C–H bending (CS_2)		
$\Delta^{13(18)}$-Compound.					
28-Norolean-13(18)-ene	—	—	—	—	—
Δ^{17}-Compounds.					
28-Norolean-17-en-3β-ol (oleanol)	—	—	—	—	—
28-Norolean-17-ene	—	—	—	—	—
28-Norolean-17-en-3-one	—	—	—	—	—
(B) Conjugated dienes.					
$\Delta^{12:18}$-Compound.					
Me 3β-acetoxyoleana-12 : 18-dien-28-oate	1650		808	819	834
$\Delta^{9(11):12}$-Compounds.					
Me 3β-acetoxyoleana-9(11) : 12-dien-28-oate	1635		—	824(130)	838(33)
Ursa-9(11) : 12-diene	1635	3037			
Oleana-9(11) : 12-diene-3 : 28-diol diacetate	1635		—	820(47)	—
$\Delta^{11:12(18)}$-Compounds.					
Me 3β-hydroxyoleana-11 : 13(18)-dien-28-oate	1626		808(12)	816(10)	—
Me 3β-acetoxyoleana-11 : 13(18)-dien-28-oate	1627		808	817	—
Oleana-11 : 13(18)-diene-3 : 28-diol diacetate	1621		—	814	—
(C) Conjugated ketones.					
Δ^{12}-$C_{(11)}$-Ketones.					
Me 3β-acetoxy-11-oxo-18-*iso*olean-12-en-28-oate	1626(80)	3023(sh)	809	—	826
Me 3β-acetoxy-11-oxo-olean-12-en-28-oate	1623(70)	—	809	—	—
Urs-12-en-11-one	1622	3025(sh)			
Me 3β-acetoxy-11-oxours-12-en-28-oate	1621(80)	3023(sh)	802(20)	817(20)	826(12)
Me 3β-acetoxy-11-oxo-olean-12-en-30-oate	1621(70)	—	806(16)	824(28)	833(28)
3β-Acetoxyurs-12-en-11-one	1619	3030(sh)			
Urs-12-ene-3 : 11-dione	1618(70)	3023(sh)			
$\Delta^{13(18)}$-$C_{(12)}$: $C_{(19)}$-Diketone.					
Me 3 : 12 : 19-trioxo-olean-13(18)-en-28-oate	1622(70)	—			
$\Delta^{20(29)}$-$C_{(30)}$-Aldehydes.					
3β-Acetoxylup-20(29)-en-30-al	1618	3080(30)			
3β-Benzoyloxylup-20(29)-en-30-al	1617	3030, 3065, 3088 †			

* Weak, incompletely resolved shoulder. † Absorption of benzenoid C–H groups of benzoate.

TABLE 2. *Frequencies (cm.$^{-1}$) of bending vibrations of methylene groups adjacent to ethylenic double bonds in pentacyclic triterpenoids* (CCl_4 *solution*).

Compound	
Δ^{12}-C=C, CH_2 at $C_{(11)}$.	
Olean-12-en-3β-yl benzoate	1436
Urs-12-en-3β-ol (α-amyrin)	1435
Olean-12-en-3β-ol (β-amyrin)	1435
Urs-12-en-3β-yl acetate	1435 *
Urs-12-en-3β-yl benzoate	1435 *
Urs-12-ene	— †
Urs-12-en-3-one	1440 ‡
$\Delta^{9(11)}$-C=C, CH_2 at $C_{(12)}$.	
Olean-9(11)-ene-3β : 28-diol diacetate	1437
Δ^{17}-C=C, CH_2 at $C_{(16)}$ and $C_{(19)}$.	
28-Norolean-17-en-3β-ol (oleanol)	1437
28-Norolean-17-ene	1437 *
28-Norolean-17-ene-3-one	1436 ‡
$\Delta^{13(18)}$-C=C, CH_2 at $C_{(12)}$ and $C_{(19)}$.	
28-Norolean-13(18)-ene	1435
Δ^{18}-C=C, no adjacent CH_2.	
No peak between 1400 and 1445 cm.$^{-1}$.	
Olean-18-ene	
Olean-18-en-3β-ol	
Olean-18-en-3β-yl benzoate	
Olean-18-ene-3β : 28-diol 3-acetate	
Olean-18-en-3β : 28 diol diacetate	

* Incompletely resolved shoulder.
† See heading of Table 1.
‡ Composite band due to methylene groups adjacent to double bond and carbonyl group; see ref. 5

TABLE 3. *Summary of frequencies (cm.$^{-1}$) characteristic of ethylenic double bonds in pentacyclic triterpenoids (peak intensities in parentheses).*

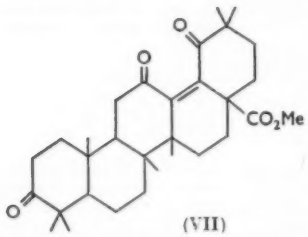
Position of unsaturation	C=C stretching	C–H stretching	C–H bending *	Adjacent CH_2
12 : 13	1650—1667(15—20)	3023—3030(sh)	804(30), 818(25), 828(30)	1435—1436
2 : 3	1659—1661(20)	3000—3010(sh)	729	
18 : 19	1645—1661(8—10)	3028—3030(sh)	802, variable	—†
9 : 11	1660	—	819(40)	1437
20 : 29	1640—1642(55—70)	3070—3072(35—45)	883(195)	—
13 : 18	—	—	—	1435
17 : 18	—	—	—	1436—1437
$\Delta^{12:18}$-Diene	1650		808, 819, 834	
$\Delta^{9(11):12}$-Diene	1635	3037	variable	—
$\Delta^{11:13(18)}$-Diene	1621—1627		808(12), 816(10)	
Δ^{12}-$C_{(11)}$-Ketone	1618—1626(70—80)	3023—3030(sh)	806, 820(?), 828	—
$\Delta^{13(18)}$-$C_{(12)}$: $C_{(19)}$-Diketone	1622(70)	—		

* Mean values, see text. † See heading of Table 1.

or more bands due to in-phase and out-of-phase vibrations of the system.[2] In the few conjugated dienes investigated here, only one band could be detected, although they were all measured in chloroform down to 1550 cm.$^{-1}$. This is not surprising in the case of the $\Delta^{11:13(18)}$-compounds where one of the double bonds is fully substituted, but a second band of lower frequency might be expected in the spectra of the other types. However, the intensity of the absorption could be very low.

The ethylenic C–H stretching band of the 9(11) : 12-diene system has been mentioned above.

(*C*) *Conjugated Ketones.*—The carbon–carbon double-bond stretching absorption of a conjugated ketone also occurs at a lower frequency than that of the non-conjugated type, and is approximately three times as intense (Table 1*C*). The degree of lowering of frequency varies from one type to another, being about 36 cm.$^{-1}$ for the Δ^{12}-$C_{(11)}$-ketones and 23 cm.$^{-1}$ for $\Delta^{20(29)}$-$C_{(30)}$-aldehydes. This lowering will be increased the more effective the conjugation, and also in the case of an endocyclic double bond if the presence of three trigonal carbon atoms leads to increased ring strain.



(VII)

The spectrum of methyl 3 : 12 : 19-trioxo-olean-13(18)-en-28-oate (VII) is interesting since it illustrates that double-bond stretching absorption can be exhibited by a fully (but not symmetrically) substituted ethylenic system. This compound, of course, has no adjacent methylene group absorption related to the ethylenic double bond.

EXPERIMENTAL

The infrared spectrometer has been previously described.[5] Compounds were studied as carbon tetrachloride (1350—3700 cm.$^{-1}$, calcium fluoride prism, single-pass) and carbon disulphide (680—1350 cm.$^{-1}$, sodium chloride prism, double-pass) solutions at approx. 0·02M concentrations in cells of 1·2 and 3 mm. thickness. Intensities, measured as peak apparent molar extinction coefficient [$\varepsilon = (\log_{10} I_0/I)/cl$], are accurate to approx. 5%, and have not been corrected for finite slit width.[16]

The infrared spectrometer was purchased through a generous grant from the Nuffield Foundation, to whom one of us (A. R. H. C.) is indebted for a fellowship. The authors thank Professor D. H. R. Barton, F.R.S., who supplied most of the compounds, and Dr. D. E. White, who provided the others. Some of this work was carried out while one of us (D. W. T.) was working under the general direction of Professor N. S. Bayliss and we thank him for his interest.

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[*Received, September 20th,* 1956.]

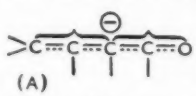
[16] Ramsay, *J. Amer. Chem. Soc.*, 1952, **74**, 72.

254. *Reduction by Dissolving Metals. Part XIV.* Some Stereochemical Aspects of the Reduction of αβ-Unsaturated Ketones.*

By A. J. Birch, Herchel Smith, and R. E. Thornton.

Theoretical aspects of the addition of cations to mesomeric anions are briefly reviewed. The stereochemistry of the process in relation to the reversible or irreversible addition of protons is discussed and extended to an examination of the expected course of reduction of certain αβ-unsaturated ketones by means of metal–ammonia reagents. The reduction of 1 : 2 : 3 : 4 : 9 : 10-hexahydro-7-methoxy-1-oxophenanthrene by lithium and ethanol in ammonia leads initially to *cis*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-7-methoxy-1-oxophenanthrene, which is convertible into the more stable *trans*-isomer.

Early in our investigations of the processes whereby unsaturated compounds are reduced by metal–ammonia reagents,[1] it became clear that the products are formed by the addition of protons to mesomeric anions which contain at least two possible reactive positions. Hence it was necessary to consider the factors influencing the choice of position in reactions of this type. Theoretical ideas were advanced [2] in 1947 on this subject, which is fundamental also for other reactions. It was pointed out that the constitution of the product depends in whether the addition is reversible or irreversible. Under reversible conditions the product is the thermodynamically stable one; under irreversible conditions it is determined by the relative rates of addition to the possible positions in which a free anionic charge can appear. In general this position appears to be that in which the charge is most stable, provided the cation requires very little energy to detach it from the molecule of which it forms a part. Essentially the same views have more recently been put forward by other workers.[3,4] The theory proved to be of great utility in indicating methods by which isomers of other than the lowest energy state can be produced, and in explaining the products obtained in the reduction of benzene rings by means of metal–alcohol–liquid ammonia reagents.[1] It proved possible to prepare an unconjugated *cyclo*hexadiene from the conjugated one,[4] and for heteroenoid systems to predict that a cation should be added irreversibly to the carbon atom β to the oxygen in an anion such as (A). This



(A)

prediction was verified by conversion of 3-acetoxycholesta-3 : 5-diene into cholest-5-en-3-one [5] through the mesomeric anion of 3-hydroxycholesta-3 : 5-diene (an essential step in the Oxford synthesis of cholesterol [6]). In more recent work on the alkylation of unsaturated ketones, *e.g.*, in the Harvard synthesis of steroids [7] and the synthesis of lanosterol,[6] the same factors are undoubtedly involved.

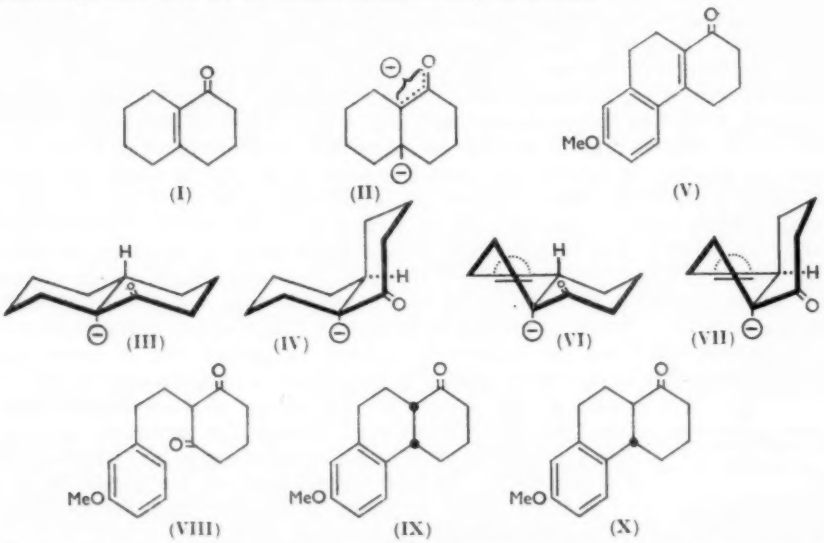
In connection with our programme of work on the synthesis of analogues of steroid hormones we have turned our attention to the problem of obtaining stereoisomers of other than the lowest energy-level by the irreversible addition of protons to the mesomeric anions formed by the reduction of polycyclic αβ-unsaturated ketones. In view of Zimmerman's recent elegant work [9] based on the same kind of ideas, but with somewhat more favourable substances, we present a preliminary account of some of our work.

* Part XIII, *Austral. J. Chem.*, 1955, **8**, 512.

[1] Birch, Part I, *J.*, 1944, 430, and subsequent papers; cf. *Quart. Rev.*, 1950, **4**, 69.
[2] Birch, *Discuss Faraday Soc.*, 1947, **2**, 246.
[3] De la Mare, Hughes, and Ingold, *J.*, 1948, 17; Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons, Ltd., London, 1953, p. 700; Kornblum, Smiley, Blackwood, and Iffland, *J. Amer. Chem. Soc.*, 1955, **77**, 6269.
[4] Birch, *J.*, 1950, 1551.
[5] Birch, *J.*, 1950, 2325.
[6] Cardwell, Cornforth, Duff, Holtermann, and Robinson, *J.*, 1953, 361.
[7] Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223.
[8] Woodward, Patchett, Barton, Ives, and Kelly, *ibid.*, 1954, **76**, 2853.
[9] Zimmerman, *ibid.*, 1956, **78**, 1168.

XUM

For discussion the simplest example is the reduction of 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-1-oxonaphthalene (I). The intermediate dianion (II) will initially add a proton to the β-anionic carbon atom, which will be highly basic. In general, when this position is capable of giving rise to stereoisomers the more stable configuration would be expected since the proton-donor normally present (ammonia, an alcohol, ammonium chloride) has pK_a far lower than that of the resulting hydrocarbon. The deciding factor will therefore be the most stable conformation of the anion, not the path of approach of the proton donor (cf. ref. 10). For the α-position other considerations apply. The enolate anion is stable under the reduction conditions unless a large excess of an "acid" is present; the pK of the enol-form should be 10—12. This stability protects the group from further reduction and permits eventual isolation of the ketone. The keto-form is produced during the isolation and its configuration will be determined by the choice between the canonical forms (III) and (IV) in the attack by the proton-donor. It is clearly seen that although the form (III) is the more stable anion, the path of approach is hindered, being axial to both rings, while in the form (IV) it is axial to one ring and equatorial to the other. Conceivably, therefore, the *cis*-ketone could initially be formed.



We have tested this hypothesis on more complex compounds *e.g.*, the phenanthrene (V), more closely related to our synthetic programme. In this case the principles involved are the same, except that the fused aromatic ring will tend to flatten the attached ring (VI; *trans*-form; VII, *cis*-form). This would be expected to reduce the difference in energy-level between the ketones * themselves without greatly affecting the relative rates of addition to the anionic charges in the enolate anions (VI) and (VII).

The ketone (V) was synthesised by a type of route already well established.[12] 3-Methoxyphenethyl bromide condensed with the potassium salt of 1 : 5-dimethoxy*cyclo*hexa-1 : 4-diene in liquid ammonia to a product hydrolysed by acid to the *cyclo*hexane-1 : 3-dione (VIII). Cyclisation of this with polyphosphoric acid gave the phenanthrene ketone (V).

* Klyne [11] has reviewed current ideas on the factors governing the relative stabilities of various stereoisomeric decalones.

[10] Barton and Robinson, *J.*, 1954, 3045.
[11] Klyne, *Experientia*, 1956, **12**, 119.
[12] Birch and Smith, *J.*, 1951, 1882.

Reduction of the ketone (V) with lithium and ethanol in ammonia under defined conditions gave an octahydro-oxomethoxyphenanthrene (IX), m. p. 68—71°, which on treatment with mineral acid or passage in light petroleum through alkaline alumina was converted into an isomer. This isomer from its m. p. (111°) is the known *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-1-oxo-7-methoxyphenanthrene (X) whose stereochemistry is established through its relation to œstrone.[13] Neither of the two compounds can be an enol, since no hydroxyl band, but the expected carbonyl band, is present in the infrared spectra. These spectra, although similar, differ significantly in the region 8—15 μ. Equilibration of the *trans*-isomer with methanolic potassium hydroxide gave a mixture whose infrared spectrum showed bands characteristic of both *cis*- and *trans*-isomers in an estimated ratio of 1 : 4. The free-energy difference is therefore, as expected, rather small (about 0·8 kcal. mole^{-1}). It is of interest that the *cis*-ketone can be purified by chromatography on the earth, " Florex," without equilibration.*

The generally accepted rule that the stable isomer predominates in the products of reduction by dissolving metal [10,11] undoubtedly holds under usual experimental conditions for carbon–carbon systems and for the β-position in αβ-unsaturated ketones. The fact that stable isomers are usually isolated from the latter must depend on the ready establishment of equilibria during isolation, for example, by chromatography on alumina.[14] It is noteworthy that the *trans*-junction was produced by reduction of an α-octalone derivative to the corresponding decalol with a large excess of lithium and ethanol in liquid ammonia.[15] In this case equilibration of the initial *cis*-decalone derivative, if formed, must have occurred before reduction of the carbonyl group.

The theoretical treatment above may need to be modified for reactions in non-polar media where effects due to proximity of the metal cation may need to be considered.

Experimental

Evaporations were carried out under reduced pressure. Light petroleum means the fraction, b. p. 60—80°. Florex is a grade of Florida fuller's earth prepared by the Floridin Co., Warren, Pennsylvania.

1 : 2 : 3 : 4 : 9 : 10-*Hexahydro*-7-*methoxy*-1-*oxophenanthrene* (V).—1 : 5-Dimethoxy*cyclo*hexadiene (60 g.) was added to a solution of potassium amide (from the metal, 8·8 g.) in liquid ammonia (500 c.c.). After 10 min. 3-methoxyphenethyl bromide (25·3 g.) in ether was added with stirring during 20 min. Water was added and the mixture extracted with ether–ethyl acetate (1 : 1; 3 × 200 c.c.). The oily product was isolated in the usual manner and treated under nitrogen with 2N-sulphuric acid on the steam-bath for 25 min. The product was dissolved in ethyl acetate, and the solution extracted portion-wise with 2N-sodium hydroxide until acidification failed to give an oil. The oil soon crystallised; it was filtered off, washed with water, and dried *in vacuo*, to give the crude 2-3′-methoxyphenethyl*cyclo*hexane-1 : 3-dione as a pale buff solid (26 g.). A portion recrystallised from ethyl acetate–light petroleum had m. p. 150°. Robinson and Schittler [16] give m. p. *ca.* 150°. The finely powdered crude dione was added to a solution of phosphoric oxide (80 g.) in phosphoric acid (*d* 1·75; 60 c.c.) and kept at 110° for 45 min. The mixture was cooled, added to water (1 l.), and extracted with ether (4 × 250 c.c.). The product was dissolved in benzene (100 c.c.) and adsorbed on alumina (200 g.). Elution with benzene (2 l.) gave the 1 : 2 : 3 : 4 : 9 : 10-hexahydro-7-methoxy-1-oxophenanthrene (12 g.), m. p. 77—78° after recrystallisation from light petroleum

* [*Added, January 29th*, 1957].—Johnson, Ackerman, Eastham, and DeWalt (*J. Amer. Chem. Soc.*, 1956, **78**, 6302) have observed that the less stable isomer is produced in the reduction of a substituted 1 : 2 : 3 : 4 : 4*a* : 9 : 10 : 10*a*-octahydro-8-methoxyphenanthrene by a metal–ammonia reagent. From an examination of models it is apparent that this result would follow from a similar kinetic control of the reduction process.

[13] Robinson and Walker, *J.*, 1936, 747; 1938, 183; Anner and Miescher, *Helv. Chim. Acta*, 1948, **31**, 2173.

[14] Cf. Ames, Beton, Bowers, Halsall, and Jones, *J.*, 1954, 1905; Bladon, Henbest, Jones, Lovell, Wood, Woods, and Elks, Evans, Hathway, Oughton, and Thomas, *J.*, 1953, 2921.

[15] Birch and Smith, *J.*, 1956, 4909.

(Found: C, 78·7; H, 7·15. Calc. for $C_{15}H_{16}O_2$: C, 78·9; H, 7·1%). Robinson and Schittler [16] give m. p. 75—76°. Light absorption in EtOH: $\lambda_{max.}$ 240·5 and 332 mμ (ε 24,000 and 12,600).

cis-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-7-*methoxy*-1-*oxophenanthrene* (IX).—The above hexahydromethoxyoxophenanthrene (10 g.) in tetrahydrofuran (250 c.c.) was added to a solution of lithium (1·4 g.) in liquid ammonia (1500 c.c.). After 10 min. ethanol was run in until the blue colour was discharged. Water was immediately added and the mixture was extracted with ether (4 × 500 c.c.). The product was an oil which was adsorbed from light petroleum–benzene (4 : 1; 100 c.c.) on Florex. Elution with light petroleum (1 l.) and recrystallisation from the same solvent gave cis-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-7-*methoxy*-1-*oxophenanthrene* (5·9 g.), m. p. 68—71° (Found: C, 78·2; H, 7·9. $C_{14}H_{18}O_2$ requires C, 78·3; H, 7·9%). The infrared spectrum had bands at 1709, 989, and 864 cm.$^{-1}$. Crystallisation of the product without chromatography gave a less pure product, m. p. 65—68°.

trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-7-*methoxy*-1-*oxophenanthrene* (X).—(*a*) The above *cis*-ketone (5·8 g.) in benzene (25 c.c.) was adsorbed on basic alumina (150 g.). Elution with benzene and recrystallisation of the product from light petroleum gave the *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-7-methoxy-1-oxophenanthrene (5 g.), m. p. 111° (Found: C, 78·4; H, 7·7. Calc. for $C_{15}H_{18}O_2$: C, 78·3; H, 7·9%). Robinson and Walker [13] give m. p. 109°. The infrared spectrum had bands at 1706 and 776 cm.$^{-1}$.

(*b*) The *cis*-isomer (IX) (0·57 g.) was refluxed in ethanol (75 c.c.) containing 6N-hydrochloric acid (18 c.c.) for 45 min. Brine (100 c.c.) was added and the product collected in ether. It was dissolved in light petroleum–benzene (1 : 1; 50 c.c.) and adsorbed on Florex (30 g.). Elution with light petroleum gave the *trans*-isomer (IX) (0·46 g.), m. p. 109° (Found: C, 78·4; H, 7·7%).

The *trans*-ketone (0·62 g.) was refluxed under nitrogen in methanol (80 c.c.) containing potassium hydroxide (0·8 g.) for 1 hr. The solution was cooled rapidly and poured into 0·2N-hydrochloric acid (220 c.c.) and extracted with ether. The product was purified by percolating its solution in light petroleum through Florex (9 g.). Its infrared spectrum had bands at 989, 864, and 776 cm.$^{-1}$, from the relative intensity of which it was estimated that the ketonic mixture contained approximately 80% of the *trans*- and 20% of the *cis*-isomer.

We thank the Essex Education Committee for a grant (to R. E. T.).

CHEMISTRY DEPARTMENT, THE UNIVERSITY, MANCHESTER. [*Received, October 3rd*, 1956.]

[16] Robinson and Schlittler, *J.*, 1935, 1288.

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255. *The Relative Stabilising Influences of Substituents on Free Alkyl Radicals. Part II.* The Addition of Aliphatic Aldehydes to ββ-Dimethylacrylic Acid and its Derivatives.*

By R. L. HUANG.

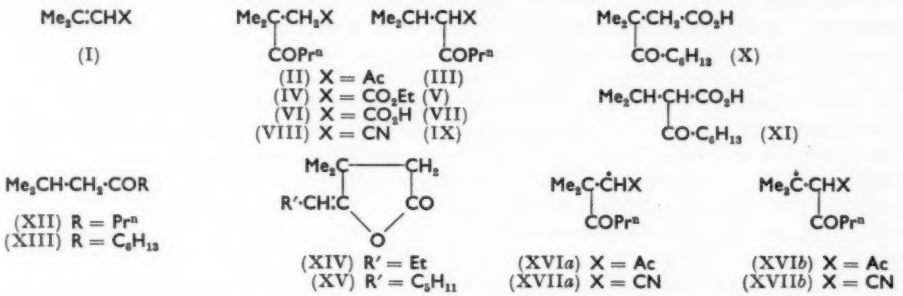
The addition of aliphatic aldehydes R·CHO (R = Pr^n and/or n-C_6H_{13}) to ββ-dimethylacrylic acid, ethyl ester, and nitrile, catalysed by benzoyl peroxide, has been studied. In each case the ratio of the isomeric adducts R·CO·CMe_2·CH_2X and Me_2CH·CHX·COR is ascertained and this provides a basis for comparing the stabilising influence of X in CMe_2:CHX on the intermediate alkyl radicals. It is thus found that CN ≈ CO > CO_2Et ≈ CO_2H. Some applications of the scale of stabilising influence obtained so far, *viz.*, Ph > CN ≈ CO > CO_2Et ≈ CO_2H > Me, are discussed.

IN Part I the homolytic addition of butanal and bromotrichloromethane to unsymmetrical olefins R·CH:CH·R′ was studied, and the mode of addition in each case afforded an intramolecular comparison of the stabilising influences of the substituents R and R′ on the free alkyl radicals. The scale of relative stabilising effects was: Ph > CN, CO_2Et; CO > CO_2Et > CO_2H > Me. We now report an intermolecular approach to the same objective, involving the addition of aliphatic aldehydes to ββ-dimethylacrylic acid and its derivatives. The results obtained in general confirm and extend previous findings.

* Part I, *J.*, 1956, 1749.

XUM

Addition of butanal to mesityl oxide (I; X = Ac) was shown by Patrick [1] to proceed with formation of the isomers (II) and (III) in a molar ratio of 10 : 1. In view of the possible presence of steric effects, and of the destabilising influence of a hydrogen atom [2] present in one of the possible intermediate radicals, *viz.*, (XVI*a* and *b*) (the initiating radical being $Pr^n\cdot\dot{C}O$),[1,3] this result cannot be interpreted as a ten-fold stabilising influence of the ketonic group compared with two methyl groups. However, addition of butanal to ethyl



ββ-dimethylacrylate (I; X = CO_2Et) has now been found to result in a 3 : 1 ratio of the isomers (IV) and (V), and, since the secondary effects just mentioned (steric and effect of a hydrogen atom) are identical in mesityl oxide and in the acrylate, the ratio of 10 : 1 against that of 3 : 1 might be used to compare the stabilising effects of the ketonic and the ester group on the intermediate radicals, *i.e.*, the former group is roughly 3·3 times as stabilising as the latter. This comparison of isomer ratios therefore constitutes an intermolecular comparison of relative stabilising capacities, in pursuance of which the addition of heptanal to ethyl ββ-dimethylacrylate and of butanal to ββ-dimethylacrylic acid (I; X = CO_2H) and to the nitrile (I; X = CN) have been investigated, benzoyl peroxide being used as the catalyst.

Addition of butanal to ethyl ββ-dimethylacrylate afforded, in good yield, a mixture of the isomeric esters (IV) and (V) (correct elemental analysis but wide boiling range), accompanied by only negligible quantities of polymer. To estimate the proportion of each ester present the mixture was hydrolysed with boiling aqueous alkali, giving the γ-keto-acid (VI) and the neutral ketone (XII) in a molar ratio of 2·7 : 1. The latter substance must have resulted from the β-keto-acid (VII) through decarboxylation, and thus the adduct mixture contained the γ- and the β-keto-ester in a ratio of approximately 3 : 1. The γ-keto-acid was found to be stable at 160°, but was converted into the unsaturated lactone (XIV) by hot acetic anhydride.

Heptanal and the same acrylic ester gave a mixture of adducts which on similar treatment with alkali yielded the unsaturated lactone (XV) and the neutral ketone (XIII) in a molar ratio of 2·9 : 1. The former was undoubtedly derived from the γ-keto-acid (X), probably by enolisation followed by dehydration during distillation, whereas the latter must have been the decarboxylated product of the β-keto-acid (XI). The ratio of γ-keto-esters is therefore again approximately 3 : 1. As before, only small quantities of polymer were encountered.

ββ-Dimethylacrylic acid gave with butanal the acid (VI) and the ketone (XII) in a molar ratio of 2·8 : 1. An unidentified neutral fraction of a wide boiling range was also produced, together with a little undistillable material.

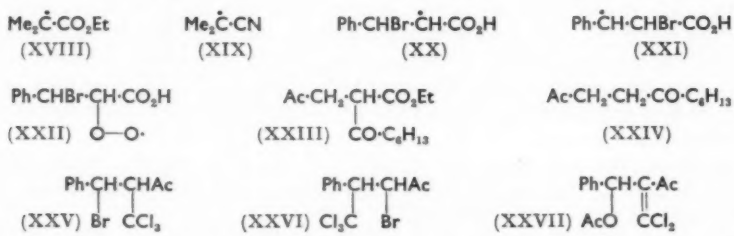
From the addition of butanal to ββ-dimethylacrylonitrile only one adduct, (VIII), was obtained (52% yield), fractionation failing to reveal any of the isomer (IX). The homogeneity of the product was confirmed by (*a*) its failure to give any of the usual tests for a

[1] Patrick, *J. Org. Chem.*, 1952, **17**, 1269.
[2] Haszeldine, *J.*, 1953, 3565.
[3] Kharasch, Urry, and Kuderna, *J. Org. Chem.*, 1949, **14**, 248; see also Patrick, *ibid.*, 1952, **17**, 1009.

keto-enol system to which the latter isomer would be expected to respond, and (*b*) its alkaline hydrolysis in a high yield (86%) to the γ-keto-acid (VI), accompanied by only negligible quantities of neutral material, which was not the ketone (XII). Absence of the nitrile (IX) is thus clearly demonstrated. Polymeric products, however, were present in considerable quantities.

The isomer ratios when X = Ac, CO_2Et, CO_2H, and CN are thus 10 : 1, 3 : 1, 3 : 1, and ∞ : 1 respectively. The results obtained for the ketonic and ester substituents more than confirm the conclusion reached in Part I, *viz.*, CO > CO_2Et; indeed, they afford a quantitative measure of the stabilising influences. Comparison of these ratios in other cases is unfortunately less decisive. It will be appreciated that, should by-products, polymeric or otherwise, of unknown precise origin, be formed to a significant extent, the isomer ratios give at best only the order of stabilising influence. This is the case with ββ-dimethylacrylic acid in which unidentified by-products are found in quantities comparable with those of the minor isomer. Consequently, although when compared with the ketonic group in mesityl oxide (ratio 10 : 1) the carboxyl group is clearly of a lower order of stabilising power, a comparison with the ester group (ratio also 3 : 1) is much less significant and gives the two substituents as probably of the same order of stabilising capacity. In Part I, the relation CO_2Et > CO_2H was based on the addition of butanal to ethyl hydrogen maleate, and, since (*a*) the yield of the main adduct was just under 50%, and (*b*) the possibility of ester-interchange under the experimental conditions could not be excluded, it seems desirable to defer a final assessment of these groups.

Again, in the addition of butanal to ββ-dimethylacrylonitrile, although the adduct (VIII) was formed to the complete exclusion of the isomer (IX), polymeric material was produced to the extent of 30% by weight of the total product. At first sight this might seem to render infeasible any comparison of the isomer ratio with other cases, since these polymers could have been derived from the less stable radical (XVII*b*), by dimerisation, or by telomerisation, *i.e.*, by attack on another molecule of the acrylonitrile. However, this is rendered improbable by the following consideration. If the polymer were produced by dimerisation of the intermediate radicals, it would be expected that the more stable radical, *i.e.*, (XVII*a*) [since (VIII) was the main adduct], would have been the main precursor,[4] and not (XVII*b*). On the other hand, if telomerisation were the mechanism involved, then, unless the unlikely assumption is made that *all* of the radicals (XVII*b*) formed reacted preferentially with the acrylonitrile, rather than attacked the butanal present in excess to give the isomer (IX), the complete absence of this isomer can be explained only by assuming that its precursor [the radical (XVII*b*)] was formed only to a very small extent if at all. It seems reasonable therefore to evaluate the cyano-group as possibly of a somewhat higher, or more probably of roughly the same, order of stabilising influence as the ketonic group.



By this approach we therefore arrive at the following scale of relative stabilising capacities: CN ≈ CO > CO_2Et ≈ CO_2H. And since, from Part I, Ph > CN and CO_2H > Me, we have Ph > CN ≈ CO > CO_2Et ≈ CO_2H > Me. This scale provides a rational

[4] Cf. Huang and Lee, *J.*, 1954, 2570.

basis on which the properties of certain free radicals and the course of many homolytic reactions can be explained, and in some cases, predicted. For example, the much greater tendency [5] of the ethoxycarbonylalkyl radical (XVIII) to disproportionate compared with the cyanoalkyl radical (XIX) is explicable in terms of the greater stabilising effect of the cyano-group. In the oxidation of cinnamic acid in the presence of atomic bromine, Brown and Daniels [6] consider the radical (XX) to be initially involved, which then with oxygen gives rise to the peroxidic radical (XXII). Waters,[7] on the other hand, prefers the intermediate (XXI), rather than (XX), although both of these satisfactorily account for the formation of the reaction products. From the now known relative stabilising influences of the phenyl and the carboxyl group, Waters's formulation is clearly correct.

Again, considering the stabilising effects of the ketonic and the ester group, the addition of heptanal to ethyl β-acetylacrylate would be expected to lead to the ester (XXIII). This has been shown to be the case by hydrolysis of the adduct, which being a β-keto-ester underwent decarboxylation as well as hydrolysis to give the 1 : 4-diketone (XXIV), identified as the pyrrole derivative formed with semicarbazide (cf. Part I). Similarly, the addition product from bromotrichloromethane and benzylideneacetone would in all probability have the structure (XXV). Although attempts to degrade the adduct to known products were not successful, this structure for it is consistent with its complete inertness towards thiourea, which would be difficult to explain on the basis of the alternative structure (XXVI), inasmuch as α-halogenoketones (*e.g.*, chloroacetone, phenacyl bromide) are known to react readily with thiourea to form aminothiazoles.[8] The unsuccessful degradative studies include (i) catalytic hydrogenation, (ii) reduction with zinc and magnesium, and (iii) treatment with potassium acetate in acetic acid, which converted the product into a partially dechlorinated substance, probably (XXVII).

Finally, in the homolytic bromination by *N*-bromosuccinimide, a process now known to result in substitution by bromine at the carbon atom which becomes the radical centre in the intermediate,[9] a substance such as β-phenylpropionic acid would be expected, in view of the dominant stabilising power of the benzene ring over the carboxyl group, to be brominated in the β- rather than the α-position. This has indeed been proved to be the case. Conversely, selective bromination by *N*-bromosuccinimide of substances containing two functional groups X and Y, such as X·$[CH_2]_z$·Y, and devoid of steric complications, should furnish yet another approach to the comparison of the stabilising capacities of such groups. Work in this direction is in progress.

Experimental

Addition of Butanal to Ethyl ββ-Dimethylacrylate.—Benzoyl peroxide (2·4 g.) was added in three portions during 24 hr. to a mixture of butanal (42 g.) and ethyl ββ-dimethylacrylate (15 g.; n_D^{23} 1·4350) at 80° under nitrogen. Heating was continued for 24 hr. more, after which unchanged butanal was removed by distillation followed by co-distillation with benzene. The product was taken up in ether, washed 5 times with 5% aqueous sodium hydrogen carbonate, once with water, dried ($MgSO_4$), and recovered. Distillation gave fractions (i) b. p. *ca.* 50°/1 mm., n_D^{23} 1·4260 (1 g.), and (ii) b. p. 90—94°/1 mm., n_D^{23} 1·4317 (14·4 g., 63%), and a residue, n_D^{23} 1·4534 (2 g.). A portion of the main fraction (ii) was distilled, giving mixed esters, b. p. 80° (bath)/0·3 mm., n_D^{23} 1·4311 (Found: C, 66·45; H, 10·3. Calc. for $C_{11}H_{20}O_3$: C, 66·0; H, 10·1%). Another portion (5·5 g.) was refluxed with 10% aqueous sodium hydroxide (30 c.c.) for 7·5 hr. The solution then being homogeneous, it was extracted with ether (4 × 25 c.c.), and the extract washed once with water. This washing, combined with the alkali fraction, was concentrated under partially reduced pressure to *ca.* 15 c.c. (in another experiment in which this was omitted troublesome emulsions were encountered in the subsequent extraction),

[5] Bickel and Waters, *Rec. Trav. chim.*, 1950, **69**, 312, 1490.
[6] Brown and Daniels, *J. Amer. Chem. Soc.*, 1940, **62**, 2821.
[7] Waters, "Chemistry of Free Radicals," 1946, Oxford Univ. Press, p. 177.
[8] *E.g.*, Traumann, *Annalen*, 1888, **249**, 38; King and Hlavacek, *J. Amer. Chem. Soc.*, 1950, **72**, 3722.
[9] Bloomfield, *J.*, 1944, 114.

then acidified with concentrated hydrochloric acid, and the acid which separated taken up in much ether and washed once with a little water. Distillation gave mainly 3 : 3-*dimethyl*-4-*oxoheptanoic acid*, b. p. 104°/0·5 mm. (2·77 g.), n_D^{24} 1·4480 (Found: C, 62·6, 62·85; H, 9·6, 9·3. $C_9H_{16}O_3$ requires C, 62·8; H, 9·4%), there being practically no residue. The 2 : 4-*dinitrophenylhydrazone*, yellow needles from aqueous ethanol, melted at 135—136° (Found: N, 15·7. $C_{15}H_{20}O_6N_4$ requires N, 15·9%); the *semicarbazone*, needles from ethanol, had m. p. 198° (Found: N, 18·05. $C_{10}H_{19}O_3N_3$ requires N, 18·3%). The neutral fraction obtained as above was practically pure *iso*butyl *n*-propyl ketone, b. p. 154—158°/755 mm. (0·73 g.), which was further distilled (b. p. 155°/755 mm., n_D^{24} 1·4098) (Found: C, 74·6; H, 12·4. Calc. for $C_8H_{16}O$: C, 74·9; H, 12·6%) (semicarbazone, m. p. 122—123°). Fournier [10] reports b. p. 155°/750 mm. and m. p. 123—124°, respectively. This ketone corresponds to 1·06 g. of the decarboxylated β-keto-acid. The ratio of the γ- : β-keto-acids is hence 2·6 : 1.

In another hydrolysis 6·0 g. of the ester mixture gave 3·84 g of the γ-keto-acid and 1·01 g. of the ketone. The ratio is therefore 2·8 : 1.

The above γ-keto-acid was stable at 160° for 2 hr., decomposing only to a small extent to the unsaturated lactone. Heating with an equal volume of acetic anhydride at 100° for 4 hr., however, converted it into 4-*hydroxy*-3 : 3-*dimethylhept*-4-*enoic lactone*, b. p. 60° (bath)/0·5 mm., n_D^{24} 1·4568 (Found: C, 70·6; H, 9·0. $C_9H_{14}O_2$ requires C, 70·1; H, 9·15%), which decolorised bromine in chloroform instantly and dissolved in 20% aqueous sodium hydroxide only after *ca.* 15 minutes' heating.

Addition of Butanal to ββ-Dimethylacrylic Acid.—The product from the acid (25·0 g.), butanal (110 g.), and benzoyl peroxide (4·8 g.) was diluted with ether and extracted with 20% aqueous sodium carbonate (5 × 30 c.c.), thus giving an aqueous solution A and an ethereal solution B. Solution A was washed with ether, acidified with concentrated hydrochloric acid, then concentrated to half its volume by distillation at 190 mm. (ββ-dimethylacrylic acid readily steam-distils under these conditions, while 3 : 3-dimethyl-4-oxoheptanoic acid does not). No dimethylacrylic acid was recovered. The solution was then extracted with ether, and the ethereal extract dried and finally distilled, giving fractions (i) b. p. 112—116°/2 mm. (8·0 g.), and (ii) 3 : 3-dimethyl-4-oxoheptanoic acid, b. p. 116—118°/2 mm., n_D^{24} 1·4498 (16 g.) (semicarbazone, m. p. and mixed m. p. 198°), and a residue (*ca.* 1 g.). Fraction (i) partially crystallised, and the supernatant liquid (4·3 g.), which was decanted, was shown to contain 88% (4·0 g.) of the same γ-keto-acid by a comparison of the yields of semicarbazone formed by a pure sample under the same conditions (2·5 g. from 2·0 g. acid). The total yield of the γ-keto-acid was therefore 20·0 g. The solid which separated from (i) was benzoic acid (*ca.* 2·7 g.; m. p. and mixed m. p. after recrystallisation from light petroleum).

Solution B was dried and concentrated, and after fractionation gave (i) *sec.*-butyl *n*-propyl ketone (5·8 g.), b. p. 154—159°/760 mm., n_D^{23} 1·4120 (semicarbazone, m. p. and mixed m. p. 123°), (ii) material, b. p. 55—104°/1 mm., n_D^{23} 1·4464 (1·4 g.), which did not react with semicarbazide and was not further investigated, (iii) more 3 : 3-dimethyl-4-oxoheptanoic acid (1·7 g.), b. p. 106—118°/1 mm., n_D^{23} 1·4496, soluble in aqueous sodium carbonate (semicarbazone, m. p. and mixed m. p. 196—197°), and (iv) an undistillable residue (2·7 g.; bath up to 160°/1 mm.).

The yield of γ-keto-acid is thus 21·7 g., against a computed yield of 7·8 g. of the decarboxyled β-keto-acid, giving a ratio of 2·8 : 1 (total yield of keto acids: 69%).

Addition of Heptanal to Ethyl ββ-Dimethylacrylate.—The reaction mixture from the acrylate (19·3 g.), heptanal (85 g.), and benzoyl peroxide (2·9 g.), after removal of excess of aldehyde under reduced pressure and of benzoic acid, gave on distillation fractions (i) b. p. 94—98°/0·5 mm. (2 g.) and (ii) 98—105°/0·5 mm. (23·5 g.; 65%), n_D^{23} 1·4382, and a residue (3·0 g.). A portion (11·4 g.) of fraction (ii) was refluxed with 10% sodium hydroxide solution (60 c.c.) for 8 hr., and the products were worked up as before, giving (*a*) *iso*butyl *n*-hexyl ketone, b. p. 160° (bath)/7 mm. (the ketone froths uncontrollably when vacuum-distilled with a capillary leak, and is best distilled evaporatively), n_D^{22} 1·4241 (1·6 g.) (Found: C, 77·6; H, 13·1. Calc. for $C_{11}H_{22}O$: C, 77·6; H, 13·0%), and (*b*) 4-*hydroxy*-3 : 3-*dimethyldec*-4-*enoic lactone*, b. p. 99—100°/0·5 mm., n_D^{23} 1·4590 (5·4 g.) (Found: C, 73·3, 73·2; H, 10·2, 10·1. $C_{12}H_{20}O_2$ requires C, 73·4; H, 10·3%). The lactone was insoluble in cold 20% aqueous sodium hydroxide, but dissolved slowly therein when warmed; it decolorised bromine instantly in chloroform. Heating it with a solution of semicarbazide in aqueous alcohol in presence of sodium acetate for 15

[10] Fournier, *Bull. Soc. chim. France*, 1910, **7**, 839.

min. and storage for 48 hr. gave 3 : 3-*dimethyl*-4-*semicarbazonodecanoic acid*, needles (from aqueous ethanol), m. p. 147—150° (Found : C, 57·4; H, 9·35; N, 15·4. $C_{13}H_{25}O_3N_3$ requires C, 57·5; H, 9·3; N, 15·5%). The yield of lactone corresponds to 5·9 g. of the γ-keto-acid, and that of the ketone to 2·0 g. of the decarboxylated β-keto-acid, giving a ratio of 2·9 : 1 (yield, 79%).

Hydrolysis of the ester mixture with 10% aqueous-ethanolic (1 : 1) potassium carbonate was incomplete (56% unchanged) after 7·5 hr.

Addition of heptanal (38 g.) to the acrylate (7·2 g.) by heating with di-*tert.*-butyl peroxide (0·88 g., 10 moles %) at 125—135° for 46 hr. gave on distillation an ester mixture, b. p. 76—98°/1 mm. (8·0 g.), n_D^{23} 1·4352, and a large undistillable residue (15·4 g., bath up to 175°/1 mm.).

Addition of Butanal to ββ-*Dimethylacrylonitrile*.—The product obtained by heating at 75° for 26 hr. butanal (94 g., 1·3 moles), the nitrile (17·0 g., 0·21 mole; b. p. 65°/56 mm., n_D^{21} 1·4332; see Felton and Orr [11]), and benzoyl peroxide (6·0 g., 0·025 mole; added in 3 portions during the first 18 hr.) was carefully fractionated through a 15 cm. Vigreux column, the following fractions being collected : (i) b. p. 50—60°/95 mm. (2·95 g.); (ii) b. p. 61°/45 mm., n_D^{21} 1·4342 (3·5 g.); (ii) b. p. 71—73°/2 mm., n_D^{21} 1·4395 (8·21 g.); and (iv) b. p. 73°/2 mm., n_D^{21} 1·4398 (2·56 g.). The Vigreux column was then replaced by an ordinary distilling head (*ca.* 4 cm.) and distillation continued to give fraction (v), b. p. 99—104°/2 mm., n_D^{21} 1·4561 (0·50 g.), a pale, somewhat viscous liquid, and (vi) an undistillable residue (5·15 g.) (bath up to 155°). Fraction (i) on distilling at atmospheric pressure through a 5 cm. Vigreux column gave benzene (0·7 g. from benzene added to co-distil with excess of butanal), the remainder being mostly unchanged ββ-dimethylacrylonitrile, which, together with fraction (ii), made a total of 5·8 g. of recovered material. Fractions (iii) and (iv) were both 3 : 3-*dimethyl*-4-*oxoheptanonitrile* (10·8 g., 52% calc. on the nitrile consumed) (Found : C, 70·6; H, 9·8; N, 9·3. $C_9H_{15}ON$ requires C, 70·55; H, 9·9; N, 9·1%). It was insoluble in 20% aqueous potassium hydroxide and did not decolorise bromine, or give a colour with ferric chloride. Its *semicarbazone*, needles from aqueous ethanol, had m. p. 183—185° (Found : N, 26·55. $C_{10}H_{18}ON_4$ requires N, 26·65%).

Hydrolysis. The above adduct (9·0 g.) was boiled under an efficient reflux condenser with 15% aqueous sodium hydroxide (75 c.c.) for 9 hr. Next day the mixture was thoroughly extracted with ether (4 × 50 c.c.). The ethereal extract was washed with water once, dried, and on evaporation gave very small quantities of a brown oil (0·18 g.), which did not react with semicarbazide. The aqueous fraction was concentrated under partially reduced pressure to *ca.* 30 c.c., acidified under cooling with concentrated hydrochloric acid, and the acid so precipitated taken up in much ether, dried, and concentrated, giving 3 : 3-dimethyl-4-oxoheptanoic acid (crude, 8·7 g., 86%) which was distilled, b. p. 106—108°/1 mm. (6·5 g.), n_D^{20} 1·4491 (semicarbazone, m. p. 200°, alone or mixed with the sample obtained previously).

Addition of Heptanal to Ethyl β-*Acetylacrylate* (with Sim Wong Kooi).—The acrylate (16·6 g.), heptanal (79 g.), and benzoyl peroxide (4 × 0·6 g.), when heated at 70° for 7 hr. and 85° for 1 hr., gave on distillation *ethyl* 2 : 5-*dioxoundecane*-4-*carboxylate*, b. p. 119—121°/1 mm., n_D^{24} 1·4481 (12·6 g., 42%) (Found : C, 65·5, 65·5; H, 9·3, 9·4. $C_{14}H_{24}O_4$ requires C, 65·6; H, 9·4%). The adduct was soluble in 30% sodium hydroxide solution, decolorised bromine instantly in carbon tetrachloride, and gave a reddish-violet colour with ferric chloride. The *semicarbazone*, leaflets from ethanol, had m. p. 184—185° (Found : N, 14·0. $C_{15}H_{25}O_3N_3$ requires N, 14·2%). A sample of the adduct (4·5 g.) was hydrolysed by potassium carbonate (5 g.) in boiling water (30 c.c.) and ethanol (20 c.c.) for 8 hr. Ethanol was removed under reduced pressure, and the neutral product taken up in ether and evaporatively distilled, to give undecane-2 : 5-dione, b. p. 90° (bath)/0·5 mm., n_D^{24} 1·4430 (*ca.* 2 g.), identified as (2-methyl-5-hexyl-1-pyrryl)urea which it formed readily with semicarbazide, m. p. 152—153° (Found : N, 18·9. $C_{12}H_{21}ON_3$ requires 18·8%).

Addition of Bromotrichloromethane to Benzylideneacetone.—Benzoyl peroxide (8 g., 24 mole %) was added in 4 portions during 12 hr. to benzylideneacetone (20 g.) and bromotrichloromethane (160 g.) at 60—65° under nitrogen. Heating was continued for 12 hr. more, the last hr. being at 90°. After removal of benzoic acid in aqueous sodium hydrogen carbonate, and excess of bromotrichloromethane under reduced pressure, addition of methanol and chilling caused the separation of 4-*bromo*-4-*phenyl*-3-*trichloromethylbutan*-2-*one* which was filtered off. It had m. p. 81—86° (20·5 g., 43%), raised to 95—97° on recrystallisation from methanol, from which it was obtained as needles (Found : C, 38·4; H, 3·1; Br, 23·2. $C_{11}H_{10}OBrCl_3$ requires C, 38·3; H, 2·9; Br, 23·2%). A small quantity of a sparingly soluble solid, m. p. 262° (decomp.) (0·25 g.),

[11] Felton and Orr, *J.*, 1955, 2172.

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was separated during the first recrystallisation, but was not further investigated. The filtrate was concentrated to a brown viscous oil (27 g.), and was heated with potassium acetate (27 g.) in glacial acetic acid (120 c.c.) at 80° for 20 hr. and then at 100° for 2 hr. After removal by distillation under reduced pressure of most of the acetic acid, the mixture was poured into water and neutralised with sodium carbonate, and the product taken up in ether, washed with water, and dried. Distillation then gave unchanged benzylideneacetone, n_D^{24} 1·5850 (*ca.* 1 g.) (semicarbazone, m. p. and mixed m. p. 182—185°), and *4-acetoxy-3-dichloromethylene-4-phenylbutan-2-one* (4·0 g.), b. p. 122—126°/2 mm., n_D^{24} 1·5420 (the refractive index is slightly too high owing to admixture with traces of benzylideneacetone. This was found to be the case whenever dehydrobromination was carried out on material containing the starting material. The solid adduct, however, gave a product with constant value for the refractive index; see below) (Found: C, 54·5; H, 4·3; Cl, 24·6. $C_{13}H_{12}O_3Cl_2$ requires C, 54·4; H, 4·2; Cl, 24·7%). Its *semicarbazone*, which crystallised from aqueous ethanol in needles, melted at 182° (Found: C, 49·3, 49·3; H, 4·2, 4·6; N, 12·0, 11·9. $C_{14}H_{15}O_3N_3Cl_2$ requires C, 48·9; H, 4·4; N, 12·2%). There was an undistillable residue (10 g.). The second fraction above (4·0 g.) corresponds to a further yield of at least 5 g. of the solid adduct, bringing the total yield to 57% or higher, based on the benzylideneacetone consumed.

Use of only 10 mole % of benzoyl peroxide and heating for 10 hr. gave 23% of unchanged benzylideneacetone and 45% of the adduct.

Degradation. (i) Reaction with potassium acetate. The above adduct (3 g.; m. p. 93—95°) was heated with potassium acetate (4 g.) in glacial acetic acid (20 c.c.) as described above. Distillation of the product gave the same acetoxybutanone, b. p. 140° (bath)/1 mm. (1·9 g., 76%), n_D^{24} 1·5350 (Found: C, 54·45; H, 4·4; Cl, 25·0%). Its semicarbazone had m. p. 182—184°, alone or mixed with the sample obtained as above. Further distillation gave fractions of the same refractive index.

Treatment with only one mol. of potassium acetate in the same way gave a partially debrominated and partially dechlorinated product.

(ii) Hydrogenation. (*a*) The adduct, in ethanol in the presence of 10% palladised charcoal and magnesium oxide (" AnalaR ") absorbed 1·1 mol. of hydrogen in 10 min., giving a hygroscopic colloidal solid. Attempts to crystallise this from the usual organic solvents failed. An attempt to distil it *in vacuo* also failed, much decomposition occurring in the final stages of heating (bath up to 160°/0·5 mm.). (*b*) With Raney nickel (of proved activity) in ethanol containing pure pyridine, there was no uptake of hydrogen. (*c*) With Adams catalyst in ethanol, two mols. of hydrogen were taken up in 20 min., giving an oil which did not produce any crystalline material after chromatography on alumina (light petroleum–benzene).

(iii) Reaction with thiourea. The adduct and thiourea, after 2·5 hr. under reflux in ethanol, were both recovered quantitatively.

(iv) Reduction with a mixture of zinc and magnesium powder in ethanol and 50% hydrochloric acid gave on distillation a mixture of halogen-containing substances and *ca.* 30% of polymer.

Wohl–Ziegler Bromination of β-Phenylpropionic Acid (with PEARL WILLIAMS).—*N*-Bromosuccinimide (recrystallised from hot water; 2·86 g., 0·016 mole) was added to a solution of β-phenylpropionic acid (3·1 g., 0·021 mole; m. p. 49—50°) in carbon tetrachloride (*ca.* 10 c.c.; " AnalaR ") and the mixture illuminated under nitrogen with a 100-w incandescent lamp. The solution, on being boiled, became pale yellow, but little or no bromine or hydrogen bromide was evolved. After 10 minutes' refluxing the mixture became homogeneous. It was cooled slightly, and the precipitated succinimide filtered off. The filtrate was further cooled, the solid (4·5 g.) which separated consisting mainly of β-bromo-β-phenylpropionic acid and a little succinimide was collected, and dissolved in chloroform, and the solution was washed twice with water, dried, and concentrated to a small volume. On addition of hot carbon tetrachloride and cooling, pure β-bromo-β-phenylpropionic acid crystallised; it had m. p. 141—142° (lit., 137°) (2·1 g., 58% calc. on the *N*-bromosuccinimide used) (Found: C, 46·95; H, 3·9. Calc. for $C_9H_9O_2Br$: C, 47·2; H, 3·9%).

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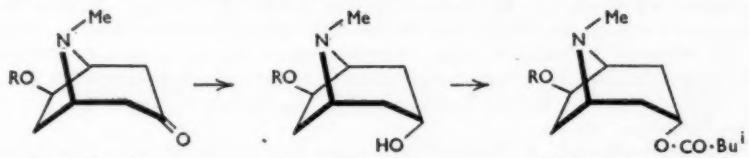
256. *The Stereochemistry of the Tropane Alkaloids. Part X.* The Total Synthesis of Valeroidine.*

By Irén Vincze, József Tóth, and Gábor Fodor.

Hydrogenation of the monophenylurethane (Ib) of 6β-hydroxytropan-3-one (Ia), followed by resolution, acylation (to IIIb), and thermolysis have led to the racemic and optically active forms of 3α-*iso*valeryloxytropan-6β-ol (IIIa).† The lævorotatory form was identical with valeroidine.

Earlier work [1] has indicated that valeroidine, an alkaloid from *Duboisia myoporoides*, is (−)-3-*iso*valeryloxytropan-6-ol (IIIa). Its alkamine was identical with the (−)-tropane-diol (IIa) from Javanese coca leaves.[2] Steric correlation of scopolamine with the racemic diol (IIa), resolution of the latter,[3] and total synthesis [4] of the racemic diol (IIa) followed. Later,[5] (+)-6β-hydroxytropan-3-one (Ia) was converted into (−)-tropane-3 : 6-diol, which was also obtained from the monoester (IIIa). However, neither selective deacylation of the di*iso*valerate of the dihydroxy-compound, nor acylation of the lævorotatory diol (IIa) gave the pure alkaloid. Formation of a lactone salt [6] from the racemic diol (IIa) supported the suggested structure for valeroidine, of which we now describe the synthesis.



(I) a: R = H b: R = CO·NHPh (II) a: R = H b: R = CO·NHPh (III) a: R = H b: R = CO·NHPh

The phenylurethane (Ib) of 6β-hydroxytropan-3-one (Ia) gave on hydrogenation tropane-3α : 6β-diol monophenylurethane (IIb). With *iso*valeryl chloride this gave the ester urethane (IIIb), which was cleaved by vacuum-distillation into (±)-valeroidine (IIIa).[7] Resolution of the phenylurethane (IIb) was preferred to that of (±)-valeroidine, and was effected by means of (+)-tartaric acid. The optically active phenylurethanes were converted into the optically active form of the monoester (IIIa), and the (−)-form proved to be identical with natural valeroidine.

Phenylurethane residues protecting hydroxyl groups have usually been removed by hydrolysis (*e.g.*,, in the case of hydroxyproline [8]), and the present thermal method deserves further examination.

Experimental

M.p.s are corrected.

(±)-6β-*Hydroxytropan-3-one Phenylurethane* (Ib).—A suspension of 6β-hydroxytropan-3-one [9] (31 g.) in ether was treated with phenyl *iso*cyanate (24 ml.) with shaking and then kept at 80° for 1 hr. The mixture was set aside for 10 hr., giving the crude product (53·8 g.), m. p. 126—129°. The contaminating diphenylurea was destroyed by the addition of N-hydrochloric

* Part IX, Fodor, Koczka, and Lestyan, *J.*, 1956, 1411.
† For nomenclature see Part I, *J.*, 1953, 721.

[1] Barger, Martin and Mitchell, *J.*, 1937, 1820; 1938, 1685; Martin and Mitchell, *J.*, 1940, 1155; Mitchell and Trautner, *J.*, 1947, 1330.
[2] Wolfes and Hromatka, *Merck's Jahresber.*, 1933, **47**, 45.
[3] Fodor, Kovács, and Mészáros, *Research*, 1952, **5**, 534; Fodor and Kovács, *J.*, 1953, 2341.
[4] Stoll, Becker, and Jucker, *Helv. Chim. Acta*, 1952, **35**, 1263.
[5] Stoll, Lindenmann, and Jucker, *ibid.*, 1953, **36**, 1506.
[6] Fodor, Tóth, and Vincze, *ibid.*, 1954, **37**, 902.
[7] Fodor, Tóth, Koczor, and Vincze, *Chem. and Ind.*, 1955, 1260.
[8] Leuchs and Brewster, *Ber.*, 1913, **46**, 986.
[9] Nedenskov and Clauson-Kaas, *Acta Chem. Scand.*, 1954, **8**, 2295.

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acid (200 ml.) in water (130 ml.). The solution was filtered, extracted with chloroform, cooled, basified with potassium hydroxide (26 g.), and extracted with chloroform (8 × 50 ml.). Drying (Na_2SO_4) and evaporation afforded the crystalline *product* (38 g., 69·5%) (Found: C, 66·0; H, 6·9; N, 10·2. $C_{15}H_{18}O_3N_2$ requires C, 65·7; H, 6·6; N, 10·2%).

(±)-*Tropane*-3α : 6β-*diol* 6-*Phenylurethane* (IIb).—The above compound (25·4 g.) was hydrogenated in dry dioxan over Raney nickel at 90 atm. for 40 hr. Part of the product separated as a white crystalline powder. It was redissolved by gentle warming, the catalyst was removed, and the solution was decolorised (charcoal) and evaporated. The *product* (22·5 g., 88%), m. p. 182° (Found: C, 65·7; H, 6·9; N, 10·1. $C_{15}H_{20}O_3N_2$ requires C, 65·2; H, 7·3; N, 10·1%), began to separate during evaporation. It was collected and washed with ether.

(±)-6β-*Phenylcarbamoyloxy*-3α-iso*valeryloxytropane* (IIIb).—*iso*Valeryl chloride (2·4 g.) was added to a suspension of the urethane (IIb) (5·5 g.) in dry chloroform (10 ml.). After 7 hr. of gentle heating the solution was evaporated to dryness, leaving an oil which crystallised on trituration with ether–acetone. The *hydrochloride* (m. p. 237°, decomp.), recrystallised from dry ethanol, had m. p. 245° (Found: C, 60·1; H, 7·65; N, 7·3; Cl, 8·8. $C_{20}H_{29}O_4N_2Cl$ requires C, 60·5; H, 7·4; N, 7·1; Cl, 8·9%).

(±)-*Valeroidine Hydrochloride* (IIIa).—(±)-Valeroidine 6β-phenylurethane hydrochloride (15·2 g.) was dissolved in water (15 ml.) by gentle warming, and the solution was adjusted to pH 10 by potassium carbonate (25 g.). The precipitated base was extracted with chloroform (6 × 50 ml.), and the dried (Na_2SO_4) extract was evaporated, giving the *base* (12·1 g.). When this was heated in a Späth tube the product distilled at 220—250°/5 mm. Nine or ten distillations completed the decomposition, and the oil thus obtained was dissolved in alcohol and treated with ethanolic hydrochloric acid. Evaporation to dryness gave a crystalline solid. Repeated recrystallisation from alcohol–ether gave (±)-*valeroidine hydrochloride* (5·85 g.), m. p. 181—183° (Found: C, 56·6; H, 8·4; N, 5·0; Cl, 12·7. $C_{13}H_{23}O_2N$,HCl requires C, 56·8; H, 8·7; N, 5·0; Cl, 12·8%).

(+)-*Tropane*-3α : 6β-*diol* 6-*Phenylurethane*.—(±)-Tropane-3α : 6β-diol 6-phenylurethane (40 g.) in alcohol (450 ml.) was treated with (+)-tartaric acid (21·2 g.) in the same solvent (150 ml.). The filtered solution was evaporated to 400 ml. and set aside overnight. A crystalline product (30·4 g.) was collected [the mother-liquor, from which the (−)-compound (IIb) was isolated, was treated as described below] and recrystallised five times from ethanol (200 ml.), giving soft needles, m. p. 182—184° (decomp.), $[\alpha]_D^{20}$ 0·0° (*c* 2 in H_2O). The solution of this salt in water (420 ml.) was basified with potassium hydroxide (32 g.) and extracted with chloroform (22 × 30 ml.). Drying (Na_2SO_4), evaporation, and washing with ether gave white crystals (9·1 g.), m. p. 203—204° $[\alpha]_D^{20}$ +7·5° (*c* 2 in dry EtOH).

(−)-*Tropane*-3α : 6β-*diol* 6-*Phenylurethane*.—The mother-liquor mentioned above was evaporated to dryness, and the residue was recrystallised from alcohol (200 ml.). The first crop of crystals (2 g.) was discarded and the residue remaining after evaporation of the mother-liquor was crystallised again. Repetition of the process six times furnished crystals of the (+)-tartrate (8·3 g.), m. p. 170—171° (decomp.), $[\alpha]_D^{20}$ +14·2° (*c* 2 in H_2O), of the lævorotatory modification.

The solution of this tartrate in water (80 ml.) was basified with potassium hydroxide (15 g.), and the organic base was extracted with chloroform (20 × 20 ml.). Evaporation of the dried (Na_2SO_4) solution yielded this base (4·95 g.), m. p. 203—204°, $[\alpha]_D^{20}$ −7·5°. A mixed m. p. with the dextrorotatory form was 182°.

(+)-6β-*Phenylcarbamoyloxy*-3α-iso*valeryloxytropane*.—*iso*Valeryl chloride (3·65 g.) was added dropwise to a suspension of (+)-tropane-3α : 6β-diol 6-phenylurethane (8·3 g.) in dry chloroform (15 ml.). After 10 hr. at 80° the solution was evaporated to dryness, leaving a residue which when rubbed with ether deposited crystals. Recrystallisation from alcohol gave the *hydrochloride* (9·2 g.), m. p. 151° (decomp.), $[\alpha]_D^{20}$ −47° (*c* 1 in H_2O) (Found: C, 60·2; H, 7·6; N, 7·1; Cl, 8·5. $C_{20}H_{28}O_4N_2$,HCl requires C, 60·5; H, 7·4; N, 7·1; Cl, 8·9%).

The enantiomer was obtained in the same way, using *iso*valeryl chloride (1·01 g.), (−)-phenylurethane (2·3 g.), and dry chloroform (4 ml.). (+)-6β-*Phenylcarbamoyloxy*-3α-iso*valeryloxytropane hydrochloride* (2·7 g.) formed crystals, m. p. 151° (decomp.), $[\alpha]_D^{20}$ +47° (*c* 2 in H_2O) (Found: C, 60·1; H, 7·7; N, 7·2; Cl, 8·7%). A mixture with the lævorotatory hydrochloride showed an elevation of m. p. to 235°.

(+)-*Valeroidine*.—A solution of (−)-6β-phenylcarbamoyloxy-3α-*iso*valeryloxytropane hydrochloride (8·5 g.) in water (40 ml.) was treated with potassium hydroxide (8 g.) and extracted

with chloroform (10 × 10 ml.). Drying (Na_2SO_4) gave an oily product (6·6 g.) (Found : C, 66·9; H, 7·7. $C_{20}H_{28}O_4N_2$ requires C, 66·6; H, 7·8%) which (5·8 g.) was submitted to thermolysis at 220—230°/4—5 mm. After ninefold distillation a smoothly crystallising oil was collected. Repeated recrystallisation from ether gave (+)-valeroidine (1·92 g.), m. p. 81°, $[\alpha]_D^{20}$ +9·0° (*c* 5 in dry EtOH), which gave with constant-boiling hydrobromic acid the *hydrobromide*, m. p. 170—171° (decomp.), $[\alpha]_D^{20}$ −5·1° (*c* 3·5 in H_2O) (Found : C, 48·0; H, 7·8; N, 4·5. $C_{13}H_{23}O_2N,HBr$ requires C, 48·45; H, 7·5; N, 4·35%), after crystallisation from ethanol.

(−)-*Valeroidine*.—(+)-6β-Phenylcarbamoyloxy-3α-*iso*valeryloxytropane (1·7 g.) was isolated from the hydrochloride as above and pyrolysed at 220—230°/4—5 mm. After tenfold distillation the product crystallised smoothly. Recrystallisation from ether gave (−)-valeroidine (0·28 g.), m. p. 81°, $[\alpha]_D^{20}$ −9·1° (*c* 2 in dry EtOH). A mixture with a natural specimen gave the same m. p. The hydrobromide obtained as above, after recrystallisation from alcohol–ether, had m. p. 170°, $[\alpha]_D^{20}$ +5·1° (*c* 3 in H_2O) (Found : C, 48·7; H, 7·9; N, 4·5%). It did not depress the m. p. (170°) of the hydrobromide prepared from natural valeroidine, for which specimen we are indebted to Dr. W. Mitchell.

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257. *Perturbation of Singlet–Triplet Transitions of Aromatic Molecules by Oxygen under Pressure.*

By D. F. EVANS.

The perturbing effect of oxygen on singlet–triplet absorption spectra has been studied quantitatively with a large number of aromatic hydrocarbons, and pressures of oxygen up to nearly 100 atm. In most cases well-defined absorption bands were observed, which disappeared on removal of the oxygen. The longest-wavelength band almost exactly coincides with the shortest-wavelength phosphorescence band in those cases where the phosphorescence emission has been studied. The only exception is 3 : 4-benzopyrene, for which the phosphorescence data may be in error. Solvent shifts of singlet–triplet transitions are very small. No comparable perturbation was observed with sulphur dioxide, and it is concluded that the effect is largely due to the paramagnetic nature of the oxygen molecule, although " charge transfer " may play some part. The nature of the stronger absorption at shorter wavelengths is also discussed.

IT was recently shown [1] that the " singlet–triplet " absorption bands around 3300 Å observed for long path-lengths of liquid benzene by Sklar,[2] Lewis and Kasha,[3] and Pitts [4] disappear when the dissolved atmospheric oxygen is removed. Conversely, they appear much more strongly in benzene saturated with pure oxygen. This was attributed to a spin-orbit perturbation [5 6] of the benzene triplet level by the inhomogeneous field of the paramagnetic oxygen molecule which effectively introduces a slight degree of singlet character into the triplet level (and, possibly, a slight degree of triplet character into the ground singlet level).

In the present work, the effect has been studied in detail for a large number of aromatic hydrocarbons, with pressures of oxygen up to nearly 100 atm.

EXPERIMENTAL

Apparatus and Procedure.—The high-pressure absorption cell consisted of a flanged brass tube fitted with two ½ in. thick plate-glass windows, each bolted between two ⅛ in. thick polytetrafluoroethylene gaskets. The effective path length was 7·2 cm. The cell was connected, *via* a

[1] Evans, *Nature*, 1956, **178**, 534.
[2] Sklar, *J. Chem. Phys.*, 1937, **5**, 669.
[3] Lewis and Kasha, *J. Amer. Chem. Soc.*, 1945, **67**, 994.
[4] Pitts, *J. Chem. Phys.*, 1950, **18**, 1416.
[5] McClure, *ibid.*, 1949, **17**, 905.
[6] Yuster and Weissman, *ibid.*, p. 1182.

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union to permit filling, to a small diaphragm valve, and the whole assembly could be fitted in the 10-cm. cell compartment of the Beckman D.U. spectrophotometer.

After the cell had been filled with solution, the absorption spectrum was first measured relative to air (or better, relative to two plate-glass windows cemented together with Silicone oil). This absorption was very small, except occasionally at the shortest wavelengths. The cell was then attached to a cylinder containing oxygen at a known pressure and shaken vigorously for about 5—6 min. Experiments showed that complete saturation was easily attained in this time. The diaphragm valve was closed, the cell disconnected, and its absorption remeasured. By subtraction the absorption spectrum resulting from the effect of the dissolved oxygen was obtained. It can be estimated from data of Horiuti [7] and Fischer and Pfleiderer [8] that the change in volume of the solution on saturation with oxygen at 75 atm. was only about 3%, and accordingly no correction was applied.

Except where otherwise stated, chloroform was used as the solvent. Chloroform is a very good solvent for aromatic hydrocarbons, and it was thought to be safer for routine use with high pressures of oxygen than such solvents as benzene or carbon disulphide. The absorption of oxygen dissolved in pure chloroform was almost negligible over the region studied (3500—8000 Å). In all cases the additional absorption observed in the presence of aromatic hydrocarbons remained constant during the period of measurement (1—2 hr.) and disappeared on removal of the oxygen.

Chemicals.—Chloroform (for analysis) was used directly, without removal of the ethyl alcohol inhibitor (~1%). Benzene (for molecular-weight determinations) was repeatedly shaken with concentrated sulphuric acid, washed, dried, and fractionally distilled. Successive fractions had almost identical ultraviolet absorption. Fluorobenzene was treated similarly. Naphthalene (for molecular-weight determinations) was once recrystallized from alcohol. Styrene, α-bromonaphthalene, and *cis*-stilbene were fractionally distilled *in vacuo*. The remaining compounds were all purified by chromatography (in benzene or light petroleum solution) through alumina or silica gel–alumina columns, and subsequent recrystallization. 9-Methylanthracene, prepared from anthrone and methylmagnesium iodide [9] and further purified *via* the picrate, had m. p. 80°. 9-Nitroanthracene, prepared as described in *Org. Synth.*,[10] had m. p. 146·5°.

Results and Discussion

The results are shown in Figs. 1—5. It can be seen that the great majority of the hydrocarbons studied give well-defined absorption bands, in addition to the rapidly rising absorption at shorter wavelengths. The longest-wavelength band for each compound is given in Table 1, together with the shortest-wavelength phosphorescence band (where known), *i.e.*, the 0, 0 band of the triplet–singlet emission spectrum. The very close agreement shows quite clearly that these bands are, in fact, the (induced) singlet–triplet absorption bands of the aromatic hydrocarbons.

The only definite discrepancy is found with 3 : 4-benzopyrene. Ilina and Shpolskii [11] reported two phosphorescence bands at 5950 and 6340 Å for 3 : 4-benzopyrene in a boric acid glass, whereas the first absorption band is at 6817 Å (Table 1 and Fig. 4). However, the Russian workers were unable to observe any phosphorescence in a low-temperature glass, and it seems very likely that decomposition had occurred as a result of the high temperature involved in the preparation of a boric acid glass and that the reported bands were due to impurities. The featureless absorption shown by diphenyl, in contrast to the well-defined phosphorescence bands starting at 4390 Å,[12] can be attributed to the various configurations adopted under different conditions owing to rotation of the benzene rings about the central bond.

In general, however, perturbation with oxygen under pressure seems a useful method for locating and confirming the triplet levels of aromatic hydrocarbons. When compared

[7] Horiuti, *Sci. Papers Inst. Phys. Chem. Res.* (*Tokyo*), 1931, **17**, No. 341, 125.
[8] Fischer and Pfleiderer, *Z. anorg. Chem.*, 1922, **124**, 61.
[9] Beckwith and Waters, *J.*, 1956, 1108.
[10] *Org. Synth.*, **31**, 77.
[11] Ilina and Shpolskii, *Izvest. Acad. Nauk S.S.S.R., Ser. Fiz.*, 1951, **15**, 585.
[12] Lewis and Kasha, *J. Amer. Chem. Soc.*, 1944, **66**, 2100.

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with the study of phosphorescence emission, it has the disadvantage that comparatively strong solutions (of the order of 1%) are required, but it is applicable in cases where no phosphorescence can be observed. The enhancement of the intensity of singlet–triplet absorption bands by oxygen seems greater (at least for unsubstituted hydrocarbons such as naphthalene) than that produced by solvents containing heavy atoms.[13]

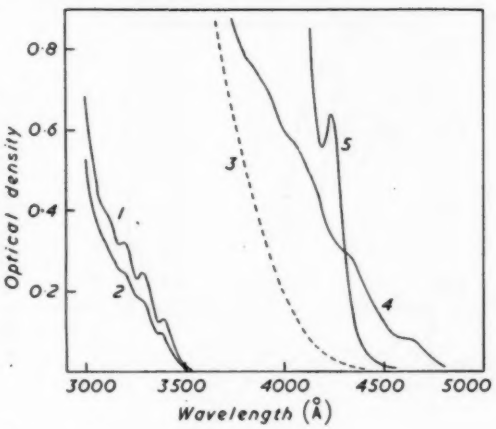

FIG. 1. 1, *Benzene, pure liquid,* 11·3M, 5-*cm. cell,* 0·89 *atm.* [*max.* (*cm.*$^{-1}$) 29,440, 30,350, 31,250, ~32,100 i]. 2, *Fluorobenzene, pure liquid,* 10·7M, 5-*cm. cell,* 0·91 *atm.* (29,500, ~30,500 i). 3, *Diphenyl,* 0·90M, ~45 *atm.* 4, *Styrene,* 0·89M, 76 *atm.* (21,600, ~23,100 i, ~24,400 i, ~25,900 i). 5, *Fluorene,* 0·90M, 76 *atm.* (23,580). *Unless otherwise stated, measurements shown in Figs.* 1—5 *were made on* $CHCl_3$ *solutions in a* 7·2-*cm. cell. Chloroform saturated at* 76 *atm. is approximately* 0·7M *with respect to oxygen.*[8]

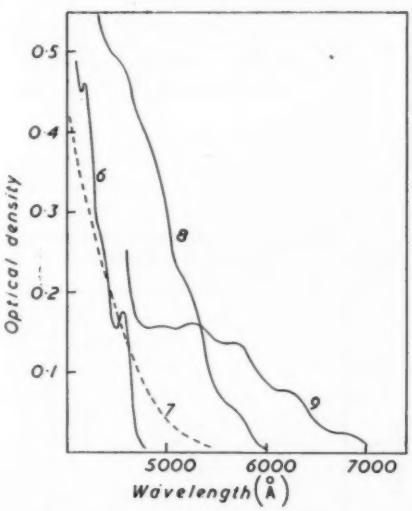

FIG. 2. 6, *Diphenylacetylene,* 0·62M, 75 *atm.* (21,860, 23,890). 7, cis-*Stilbene,* 0·53M, 76 *atm.* 8, trans-*Stilbene,* 0·72M, 76 *atm.* (17,750 i, ~19,100 i, ~20,600 i, ~22,200 i). 9, *Diphenylbutadiene,* 0·25M, 76 *atm.* [~14,700 (?), 16,180, 17,670, 18,960, 20,260].

Intensities.—The dependence of the intensity of absorption on both the oxygen pressure and the concentration of hydrocarbon was studied with naphthalene. Measurements at various pressures showed that the shape of the curve was independent of the oxygen pressure (within ±1%), and accordingly only the results for the shortest-wavelength naphthalene band at 4160 Å are plotted in Fig. 6. The optical density is approximately proportional to the oxygen pressure, although there seems to be a slight falling off at the higher pressures. This effect is, however, little greater than the experimental errors. The optical density is also directly proportional to the concentration of naphthalene (Table 2). The results for a 0·9M-solution of naphthalene are also in agreement, although a slight change in the solubility of the oxygen might be expected.

[13] Kasha, *J. Chem. Phys.*, 1952, **20**, 71.

FIG. 3. 10, *Naphthalene*, 0·90M, 76 *atm.* (21,180, 21,670, 22,600, 24,020). 11, *α-Bromonaphthalene*, 2·5M, *no* O_2, 10-*cm. cell.* 12, *α-Bromonaphthalene*, 0·50M, 75 *atm.* (20,650, 21,110, 22,100, 23,470, 24,810). 13, *Phenanthrene*, 1·01M, ~47 *atm.* (21,600, 21,970, 23,040, 24,500). (The numerals on the right-hand sign are $10^3\varepsilon$ for the broken curve.)

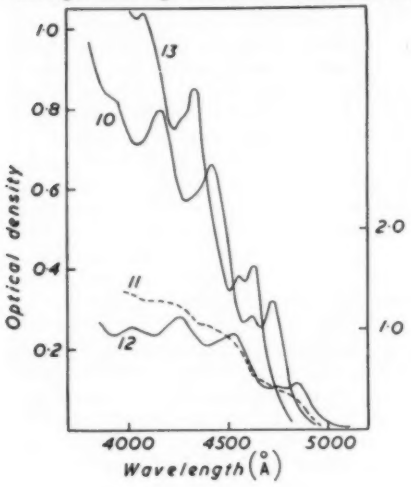

FIG. 4. 15, *Fluoranthene*, 0·91M, 76 *atm.* (18,450, 19,010, 19,940, 20,410, 21,420). 16, 1 : 2-3 : 4-*Dibenzanthracene*, 0·075M, 76 *atm.* (17,790, 19,180, 20,510, ~21,980). 17, *Pyrene*, 0·89M, ~50 *atm.* (16,930, 17,280, 18,470. 19,820, 21,370). 18, 3 : 4-*Benzopyrene*, 0·103M, 76 *atm.* (14,670, 16,190, 17,540, 18,960).

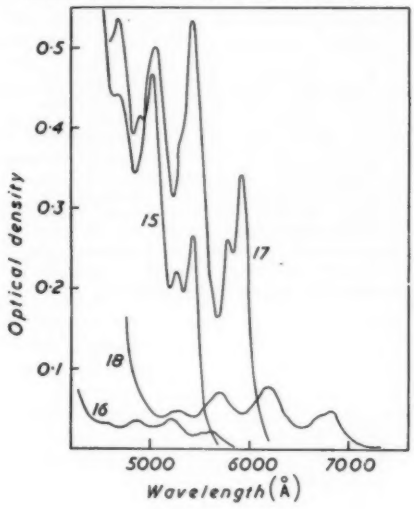

FIG. 5. 19, *Acridine*, 0·90M, ~75 *atm.* (15,840, 17,240, 18,640, 20,040, 21,430). 20, *Anthracene*, 0·087M, ~93 *atm.* (14,870, ~15,250 i, 16,300, 17,690, 19,080). 21, 9-*Nitroanthracene*, 0·25M, 75 *atm.* (14,630, 16,000, 17,360). 22, 9-*Methylanthracene*, 0·69M, 76 atm. (14,460, ~14,850 i, 15,840, 17,250, 18,660). 23 (– – – –), 9-*Methylanthracene*, 0·70M, 0·65M-SO_2, 10-*cm. cell.*

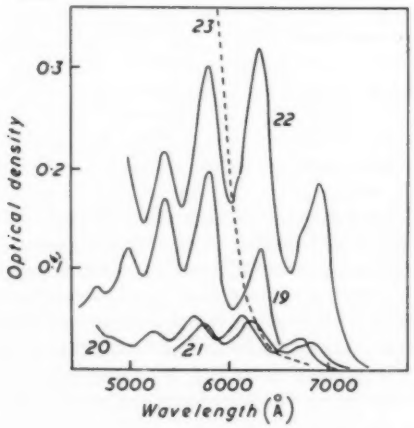

FIG. 6. *Dependence of absorption on oxygen pressure.* 0·9M-*Solution of naphthalene in chloroform;* 4160 Å *peak.*

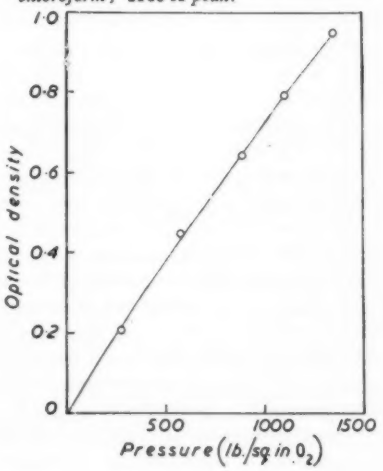

TABLE 1. *Triplet levels (cm.$^{-1}$) of aromatic molecules obtained from oxygen perturbation and phosphorescence spectra respectively.*

Compound	Oxygen perturbation ($CHCl_3$ soln.*)	Phosphorescence (low-temp. glass)
Benzene	29,440	29,470 [a]
Fluorene	23,580	23,750 [b]
Phenanthrene	21,600	21,600 [b]
Naphthalene	21,180	21,246 [b]
Fluoranthene	18,450	—
1 : 2-3 : 4-Dibenzanthracene	17,790	—
Pyrene	16,930	16,940,[11] 16,800 [b]
Anthracene	14,870	14,927 [a]
3 : 4-Benzopyrene	14,670	(16,810 [11] †)
Acridine	15,840	—
Styrene	21,600	—
trans-Stilbene	17,750	—
Diphenylacetylene	21,860	—
Fluorobenzene	29,500	—
α-Bromonaphthalene	20,650	20,700 [11]
9-Nitroanthracene	14,630	—
9-Methylanthracene	14,460	—

* Accuracy probably about 50 cm.$^{-1}$ for the condensed-ring hydrocarbons (and diphenylacetylene), and about 100—200 cm.$^{-1}$ for the other hydrocarbons.

† In boric acid glass, see text.

[a] Shull, *J. Chem. Phys.*, 1949, **17**, 295. [b] Ferguson, Iredale, and Taylor, *J.*, 1954, 3160. [c] Padhye, McGlynn, and Kasha, *J. Chem. Phys.*, 1956, **24**, 588.

TABLE 2. *Effect of concentration of naphthalene on absorption.*

Wavelength (Å)			4723	4614	4424	4164	4000
Optical density (1120 lb./sq. in. O_2)	0·25M	.....	0·175$_5$	0·153$_5$	0·358$_5$	0·436	0·409$_5$
	0·50M	.....	0·091$_5$	0·081	0·183	0·224	0·212
Ratio			1·95	1·95$_5$	1·99	2·01	2·02

These results show that experiments made under different conditions of oxygen pressure and hydrocarbon concentration can be compared (after correction) with fair accuracy. Then, when any necessary allowance is made for the background, non-triplet, absorption, it is found that the induced triplet bands of all the unsubstituted condensed-ring hydrocarbons studied differ only slightly in intensity (by a factor of about two).

As a result of the perturbing effect of the heavy bromine atom in α-bromonaphthalene, very weak singlet–triplet bands can be detected in the absence of oxygen (Fig. 3; cf. McClure, Blake, and Hanst [14]). In spite of this, the effect of dissolved oxygen is less than with naphthalene, indicating that the two types of perturbation do not particularly reinforce each other. It is also noteworthy that acridine and 9-nitroanthracene give much weaker bands than anthracene or 9-methylanthracene.

Solvent Shifts of Triplet Bands.—Since the triplet bands are normally very sharp, it is possible, with the aid of oxygen perturbation, to study accurately the effect of various solvents on their position. This has been done with naphthalene, in four solvents of widely differing refractive indices, *n*-hexane (n_D 1·38), chloroform (n_D 1·45), benzene (n_D 1·50), and carbon disulphide (n_D 1·63). (The refractive indices of the 0·9M-solutions used will be slightly different.) The results are in Table 3.

These solvent shifts are very small, appreciably smaller in fact than the usual shifts for singlet–singlet transitions, even those of comparatively low intensity.[15] That the energies of singlet–triplet transitions are relatively independent of external conditions is further indicated by the close agreement between the two columns in Table 1.

Vibrational Structure.—The triplet-state vibrational frequencies which appear (as progressions or combination frequencies) in the singlet–triplet absorption spectra are determined by symmetry conditions, and the change of molecular geometry on excitation.[16]

[14] McClure, Blake, and Hanst, *J. Chem. Phys.*, 1954, **22**, 555.
[15] Coggeshall and Pozefsky, *ibid.*, 1951, **19**, 980; Bayliss and Hulme, *Austral. J. Chem.*, 1953, **6**, 257.
[16] McClure, *J. Chem. Phys.*, 1956, **24**, 1; also refs. *a* and *b* of Table 1.

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Two such frequencies (of ~1400 and ~400—500 cm.$^{-1}$) are normally observed with the condensed-ring hydrocarbons studied, the former being especially prominent. Similar frequencies are also prominent in the phosphorescence spectra [12, 17] and in many of the singlet–singlet absorption spectra.[16 18] Low-temperature measurements of singlet–triplet spectra perturbed by oxygen might be of interest, since the vibrational structure would almost certainly be better resolved, but involve appreciable experimental difficulties.

TABLE 3. *Solvent shifts (cm.$^{-1}$) of naphthalene bands (to lower frequencies) relatively to* n-*hexane.*

Band position (*n*-hexane)	Shifts		
	Chloroform	Benzene	CS_2
21,190	20	40	120
21,690	10	30	110
22,600	0	20	100
24,020	0	10	—

For hydrocarbons having low-lying triplet levels, where the background non-triplet absorption is small, the second band is normally the most intense, and the maximum absorption (with smoothed-out vibrational structure) lies at a frequency about 2000 cm.$^{-1}$ greater than that of the first (0, 0) band.

Positions of Triplet Levels.—The triplet levels of anthracene and its derivatives as found by oxygen perturbation are in complete agreement with the recent work of Padhye, McGlynn, and Kasha.[19] These workers showed that the earlier results of Lewis and Kasha on the phosphorescence of anthracene,[12] which had been called into question by Reid,[20] were in fact correct. However, one rather puzzling discrepancy was found. Padhye, McGlynn, and Kasha claimed that the absorption spectra of anthracene (0·084M in CS_2; 20-cm. cell) showed weak singlet–triplet absorption bands. In an attempt to check this, since a 20-cm. cell was not available, a (deoxygenated) 2·3M-solution of 9-methylanthracene in purified carbon disulphide was examined in a 10-cm. cell. In spite of the 13-fold increase in (concentration × path length) no bands were observed, and the weak absorption obtained, which may be partly due to impurities, was only about one-third of that recorded for anthracene (ε of 9-methylanthracene: 0·0004, 14,500 cm.$^{-1}$; $0{\cdot}0007_6$, 15,500 cm.$^{-1}$; 0·0013, 16,500 cm.$^{-1}$; 0·0017, 17,500 cm.$^{-1}$). Since 9-methylanthracene perturbed by oxygen gives very well-defined triplet bands, and the unperturbed singlet–triplet absorption should be very similar to that of anthracene, it seems likely that the anthracene bands do not represent the true singlet–triplet absorption intensity. The life-time of the anthracene triplet state [21] in a rigid glass is less than 0·1 sec., but the intrinsic life-time in the absence of any competing radiationless processes is probably considerably greater (cf. Gilmore, Gibson, and McClure [22]).

Although the two lowest singlet states of anthracene and acridine are almost identical in energy,[23] it may be noted that the triplet bands of acridine lie at considerably shorter wavelengths than those of anthracene (Fig. 5).

The observed triplet level for 1 : 2-3 : 4-dibenzanthracene is in quite good agreement with that calculated by Hall [24] (obs. 17,790 cm.$^{-1}$; calc. 18,250 cm.$^{-1}$).

Mechanism of "Oxygen" Effect.—As mentioned in the introduction, this effect has been attributed to the paramagnetism of the oxygen molecule. However, Reid [20, 25] has

[17] Ref. *b* of Table 1.
[18] Friedel and Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, New York, 1951.
[19] Ref. *c* of Table 1.
[20] Reid, *J. Chem. Phys.*, 1952, **20**, 1212, 1214.
[21] Craig and Ross, *J.*, 1954, 1589.
[22] Gilmore, Gibson, and McClure, *J. Chem. Phys.*, 1952, **20**, 829.
[23] Badger, Fearce, and Pettit, *J.*, 1951, 3199.
[24] Hall, *Proc. Roy. Soc.*, 1952, *A*, **213**, 113.
[25] Moodie and Reid, *J. Chem. Phys.*, 1954, **22**, 252.

shown that the emission spectra of trinitrobenzene–aromatic hydrocarbon complexes closely resemble the phosphorescence spectra of the parent aromatic hydrocarbons,* but have much shorter lifetimes. This reduction in life-time was attributed to the effect of "charge transfer" in the complex on the symmetry of the π-electrons of the aromatic hydrocarbon. Since there is evidence for charge-transfer complex formation between oxygen and organic compounds,[26,27] the effect of sulphur dioxide on 9-methylanthracene was studied. Although sulphur dioxide almost certainly forms stronger complexes with aromatic hydrocarbons than does oxygen,[28] no singlet–triplet bands were observed and the absorption in the region of the first triplet band of 9-methylanthracene was very small (Fig. 5). It therefore seems very likely that the most important feature of the oxygen molecule responsible for the perturbation of singlet–triplet transitions is in fact its paramagnetic nature.

This does not necessarily mean that charge-transfer effects play no part at all. Thus, as mentioned above, the induced triplet bands are much less intense with 9-nitroanthracene and acridine than with anthracene or 9-methylanthracene. The substitution of a nitro-group, or of ·N: for ·CH:, will considerably reduce the π-donor characteristics of the anthracene molecule. Further, the perturbing effect of oxygen seems greater than would be expected from its magnetic moment, when compared with the effect of the Gd^{3+} ion (as obtained from the phosphorescence life-times of the gadolinium, lanthanum, and lutecium complexes of dibenzoylmethane).[6] It is significant that two (triplet) oxygen molecules interact to form a very weak O_4 complex, which is either diamagnetic or very feebly paramagnetic.[29] Simultaneously, the extremely weak $^3\Sigma$–$^1\Sigma$ and $^3\Sigma$–$^1\Delta$ transitions are greatly enhanced in intensity.[30] A study of the perturbing effect of other paramagnetic substances on the singlet–triplet absorption bands of aromatic molecules might prove of interest.

In the presence of oxygen under pressure, the majority of aromatic hydrocarbons studied give rise to strong absorption at wavelengths shorter than the singlet–triplet absorption bands. This absorption was previously observed with a variety of aromatic compounds and oxygen at atmospheric pressure,[26] and is also found (at still shorter wavelengths) with non-aromatic compounds such as saturated hydrocarbons, alcohols, and ethers.[26,27] Although it is possible that this more intense absorption is due to a magnetic perturbation of a higher triplet level of the organic molecule,[1] it seems much more likely that a charge-transfer transition is involved. It is not certain whether definite oxygen complexes are present, or whether the charge–transfer transition occurs between two adjacent molecules in the absence of complex formation (cf. Evans,[31] Mulliken [32]). General considerations, and a comparison of the solubilities of oxygen and nitrogen in organic solvents,[33] indicate that the latter view is probably correct for compounds such as the saturated hydrocarbons, and possibly even for many aromatic substances. The quantitative measurements on naphthalene described above, and those of Munck and Scott [27] on *cyclo*hexane (which were interpreted in terms of complex formation) are consistent with this.

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* This is not, however, true for anthracene.[19]

[26] Evans, *J.*, 1953, 345.
[27] Munck and Scott, *Nature*, 1956, **177**, 587.
[28] Andrews and Keefer, *J. Amer. Chem. Soc.*, 1951, **73**, 4169.
[29] Lewis, *ibid.*, 1924, **56**, 2027.
[30] Ellis and Kneser, *Z. Physik*, 1933, **86**, 583.
[31] Evans, *J. Chem. Phys.*, 1955, **23**, 1424.
[32] Mulliken, *Rec. Trav. chim.*, 1956, **75**, 845.
[33] Seidell, "Solubility of Inorganic and Metal Organic Compounds," Van Nostrand, 1940; Supplement, 1952; McKeown and Hibbard, *Analyt. Chem.*, 1956, **28**, 1490; Glendinning and Bedwell, Royal Aircraft Establishment, Chem. Rept. 477, 1951.

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258. *Chemical Action of Ionising Radiations in Solution. Part XX.* Action of X-Rays* (200 kv) *on Ethanol in Aqueous Solution.*

By G. G. Jayson, G. Scholes, and J. Weiss.

The action of *X*-rays (200 kv) on ethanol in aqueous solution in the presence of oxygen gave only acetaldehyde; in deaerated solutions, butane-2 : 3-diol was also produced. Quantitative studies have been carried out under various experimental conditions and the effects of pH and concentration of the solute have been examined.

A mechanism for the radiation chemistry of aqueous-ethanol solutions in the presence and in the absence of oxygen has been proposed. The detailed study of this system has led to some new aspects regarding the modes of formation of hydrogen peroxide from OH radicals in aqueous systems.

In deaerated ethanol solutions, a feature of interest is the importance of the dehydrogenation of ethanol by hydrogen atoms: $CH_3{\cdot}CH_2{\cdot}OH + H \longrightarrow CH_3{\cdot}CH(OH) + H_2$.

The chemical effects of ionising radiations in dilute aqueous solutions are due, primarily, to the net process,[1] $H_2O \rightsquigarrow H + OH$, and, with hard *X*-rays, to a smaller extent,[2] to $2H_2O \longrightarrow H_2 + H_2O_2$. The study of aqueous systems of organic compounds [3] may yield more information about the primary processes since in inorganic systems the same product is often formed by different routes. This became increasingly apparent in our studies of aqueous ethanol, the results of which are now presented.

Irradiation with *X*-rays [4] or ^{60}Co γ-rays [5] of aqueous ethanol leads to acetaldehyde, the yield of which is greater when dissolved oxygen is present. Some effects of γ-rays on aqueous methyl alcohol have been briefly reported by McDonell; [6] in deaerated solutions, formaldehyde and ethylene glycol have been found.

Results

Experiments in the Presence of Oxygen.—In ethanol solutions irradiated in the presence of molecular oxygen, acetaldehyde was the only detectable oxidation product; tests for acetic acid, butane-2 : 3-diol, ethylene glycol, glycolaldehyde, ethyl hydroperoxide, diethyl peroxide, peracetic acid, and ethyl acetate were negative.

The dependence of the yields of acetaldehyde and of hydrogen peroxide on radiation dose was investigated. $3{\cdot}4 \times 10^{-2}$M-Ethanol (100 ml.; pH 1·2), saturated with oxygen (1 atm.), was irradiated at 18—20° with *X*-rays in Pyrex glass vessels similar to those previously described.[7] Up to total doses of about 5×10^{-6} ev/*N* per ml., the yields of acetaldehyde and hydrogen peroxide were linear functions of dose and were $G(H_2O_2) = 4{\cdot}15$ and G(acetaldehyde) = 2·6 (G = molecules/100 ev).

With air-equilibrated ethanol solutions at pH ~1, it is known that, after a certain dose, a change ("break") in the rate of hydrogen peroxide formation occurs, owing presumably to the exhaustion of the dissolved molecular oxygen in the solution. With these ethanol solutions, although the air "break-point" was very marked, no satisfactory reproducibility could be obtained in this particular region; as the exact position of the break-point is controlled by the amount of dissolved oxygen and this in turn depends on the temperature, it seemed likely that the absence of efficient temperature control was the responsible factor. This was confirmed by the following experiments in which a constant-temperature irradiation vessel was used, water from a thermostat being passed around an outside jacket both before and during the irradiation. The experiments were then fully reproducible. Fig. 1 shows the yield–dose plot from irradiations of air-equilibrated ethanol solutions ($3{\cdot}4 \times 10^{-2}$M; pH 1·2) at 25°; similar measurements

* Part XIX, *J.*, 1957, 301.

[1] Weiss, *Nature*, 1944, **153**, 748; *Brit. J. Radiol.*, Suppl. 1, 1947, 56.
[2] Allen, *Ann. Rev. Phys. Chem.*, 1952, **3**, 57.
[3] Cf. Johnson, Scholes, and Weiss, *Nature*, 1956, **177**, 883.
[4] Jayson, Ph.D. Thesis, Durham, 1954.
[5] Swallow, *Biochem. J.*, 1953, **54**, 253.
[6] McDonell, *J. Chem. Phys.*, 1955, **23**, 208.
[7] Farmer, Stein, and Weiss, *J.*, 1949, 3241.

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have also been carried out at 15° and 33°.[4] Included in these Figures are some acetaldehyde and peroxide yields from the irradiation of oxygen-saturated solutions at the same temperature. It can be seen that, at a given temperature, the initial yields of acetaldehyde and hydrogen peroxide are the same in air and in oxygen-saturated solutions. However, in the air-equilibrated systems, the peroxide yields begin to fall off before the break-point is reached. This fall-off is more marked at the lower temperatures and accounts for the fact that the maximum quantities of peroxide produced ($2{\cdot}45$, $2{\cdot}74$, and $2{\cdot}92 \times 10^{-7}$ moles/ml. at 15°, 25°, and 33° respectively) increase with increasing temperature whereas, of course, the amounts of dissolved oxygen decrease.

Decomposition of hydrogen peroxide after the break-point can be attributed to, *e.g.*, the reaction, $H_2O_2 + H \longrightarrow H_2O + OH$. As long as any dissolved molecular oxygen is present, the

FIG. 1. *Irradiation of aqueous solutions of ethanol* ($3{\cdot}4 \times 10^{-2}$M, pH 1·2) *with X-rays* (200 kv). (Temp. 25°.)

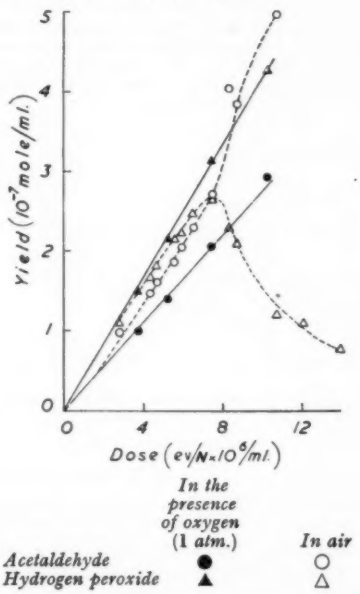
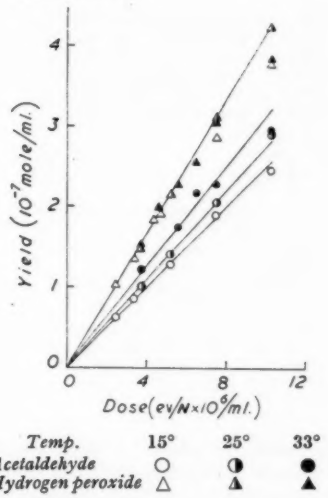


FIG. 2. *Irradiation of aqueous solutions of ethanol* ($3{\cdot}4 \times 10^{-2}$M, pH 1·2) *with X-rays* (200 kv) *in the presence of oxygen* (1 atm.).



H atoms can be removed, to a greater or lesser extent, by the process $H + O_2 \longrightarrow HO_2$. The differences between the hydrogen peroxide yields in air and in oxygen, before the break-points, can be the result of competition between molecular oxygen and hydrogen peroxide for the available hydrogen atoms; the greater disparity between the values in air and oxygen at the lower temperatures may, perhaps, be associated with a lower rate of diffusion of oxygen into local regions of oxygen depletion.

Since reduction of a peroxide molecule leads to formation of an OH radical this can lead to increased attack on the ethanol and hence to increased yields of acetaldehyde. It can be seen (Fig. 1; and similarly from the curves obtained at 15° and 33°) that in air, after the break points, the decrease in the hydrogen peroxide is accompanied by an increased formation of acetaldehyde. From these results it can be shown that the G values for peroxide decay and for acetaldehyde formation, at the maximum, are both approximately 7.

These general conclusions were substantiated by experiments in which the conditions prevailing immediately after the break-point were simulated. Ethanol solutions ($3{\cdot}4 \times 10^{-2}$M; pH 1·2) containing added hydrogen peroxide, in amounts expected in the air-equilibrated solutions at the break-point, were evacuated and irradiated with X-rays: Table 1 shows some of the results. Peroxide rapidly decayed with simultaneous formation of acetaldehyde, the G values for these processes approximating to those observed in air-saturated solutions after

the break. It should be pointed out that from these observations alone it is not possible to decide between the mechanism outlined above and a corresponding one in which the rôle of the hydrogen atom is taken by the alcohol radicals formed by reaction (1).

TABLE 1. *Irradiation with* X-*rays* (200 kv) *of evacuated ethanol solutions* ($3{\cdot}4 \times 10^{-2}$M, pH 1·2) *containing added hydrogen peroxide* ($2{\cdot}6 \times 10^{-7}$ *mole/ml.*).

Dose (ev/$N \times 10^4$/ml.)	1·68	3·15	6·30
H_2O_2 decomposed * (G)	7·35	5·90	4·09
CH_3·CHO formed (G)	7·75	4·95	5·06

* Allowance is made here for the formation of hydrogen peroxide ($G = 0{\cdot}6$) due to the process $2H_2O \longrightarrow H_2 + H_2O_2$.

It was important to establish whether or not all the available oxygen in the air-saturated solutions was eventually reduced to hydrogen peroxide or if some of its was incorporated in other products. For this purpose it was necessary to establish the exact position of the break-point. This lies on the downward slope of the peroxide decay curves (cf. Fig. 1) and is

FIG. 3. pH-*Dependence of the* initial *yields of acetaldehyde* (●) *and of hydrogen peroxide* (▲) *on irradiation of aqueous solutions of ethanol* ($3{\cdot}4 \times 10^{-2}$M) *with* X-*rays* (200 kv) *in the presence of oxygen* (1 *atm.*).

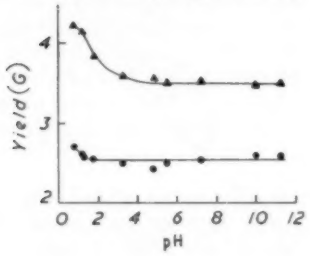
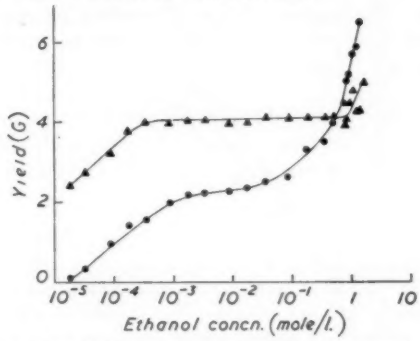


FIG. 4. *Dependence of yield on concentration of ethanol in aqueous solutions irradiated with* X-*rays* (200 kv) *in the presence of oxygen* (1 *atm.*). (pH = 1·2. *Temp.* = 20°. *Total dose* = $3{\cdot}15 \times 10^{-6}$ ev/N *per ml.*)



● *Acetaldehyde.* ▲ *Hydrogen peroxide.*

approximated by the dose at which maximum peroxide decay takes place; thus at 15°, 25°, and 33° the break-points may be taken as occurring after doses of 10·0, 8·2, and $8{\cdot}0 \times 10^{-6}$ ev/N per ml. respectively. If no decomposition had occurred before the break-points, the maximum yields of peroxide expected here would have been identical with those in solutions saturated with oxygen, *viz.*, 3·80, 3·42, and $3{\cdot}34 \times 10^{-7}$ mole/ml. at the respective temperatures. The amounts of oxygen present in solutions saturated with air at 15°, 25°, and 33° are 3·13, 2·60, and $2{\cdot}26 \times 10^{-7}$ mole/ml. respectively. It is evident that, in addition to the hydrogen peroxide obtained from this molecular oxygen, there is some excess of hydrogen peroxide corresponding to $G \simeq 1{\cdot}2$.

Plots of the peroxide and aldehyde yields from oxygen-saturated solutions ($3{\cdot}4 \times 10^{-2}$M-ethanol; pH 1·2) irradiated at 15°, 25°, and 33° are given in Fig. 2 which shows that, whereas the yield of peroxide is practically independent of temperature over the range studied, at $G(H_2O_2) = 4{\cdot}15$, the formation of aldehyde increases with increasing temperature: at 15°, 25°, and 33°, G(aldehyde) equals 2·5, 2·75, and 3·1 respectively. Although the extent of this temperature dependence would not be very marked over the normal working range (18—20°), all subsequent experiments were conducted at controlled temperatures.

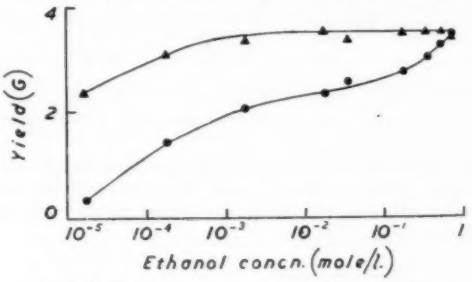
It may be pointed out that the initial G values of the reaction products were independent of the dose-rate over the range $0{\cdot}9$—$2{\cdot}7 \times 10^{-7}$ ev/N per ml. per min. and were not influenced by the presence of the water-jacket around the irradiation vessel.

The dependence on pH of the yields of acetaldehyde and hydrogen peroxide in oxygen-saturated ethanol solutions ($\sim 10^{-2}$M) were studied over the pH range ~1—11. From a series of yield–dose plots, the influence of pH on the initial yields could be examined. The results (Fig. 3) show that, under these conditions, G(acetaldehyde) is relatively constant (= 2·55) over

the greater part of the pH range, except in the more strongly acid solutions where there is a slight increase. Over a wide range above pH ~4, $G(H_2O_2) = 3{\cdot}5$, but below this pH, it increases up to G ~4·2 at pH ~0·8. Since the additional absorption of X-rays in these solutions amounts only to about 1%, it is apparent that increase in the hydrogen-ion concentration has a definite effect on the formation of hydrogen peroxide at this solute concentration.

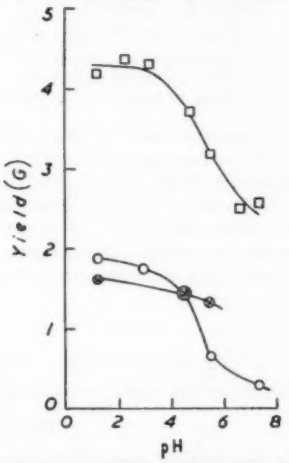
The dependence of the yields of acetaldehyde and hydrogen peroxide on the concentration of ethanol in solutions irradiated in the presence of oxygen at pH 1·2 and at pH 5·4 is shown in Figs. 4 and 5. A low dose (~3×10^{-6} ev/N per ml.) was used in order to avoid the possibility

FIG. 5. *Dependence of yield on concentration of ethanol in aqueous solutions irradiated with* X-*rays* (200 kv) *in the presence of oxygen* (1 *atm.*). (pH = 5·4. *Temp.* = 20°. *Total dose* = $3{\cdot}15 \times 10^{-6}$ ev/N *per ml.*)



● *Acetaldehyde.* ▲ *Hydrogen peroxide.*

FIG. 6. pH-*Dependence of the initial yields of acetaldehyde* (○), *of hydrogen* (□), *and of butane-2 : 3-diol* (⊕) (*total dose* = $3{\cdot}15 \times 10^{-6}$ev/$N$ *per ml.*), *on irradiation of aqueous solutions of ethanol* ($3{\cdot}4 \times 10^{-2}$M) *with* X-*rays* (200 kv) in vacuo.



of secondary processes, and this was found to be sufficient to determine the initial yields in solutions down to 10^{-4}M-ethanol. The following facts emerge from these experiments:

(*a*) Over the whole concentration range studied the yields of acetaldehyde never become independent of the solute concentration. The relative increase in the oxidation yields is greatest in the lower region, that is, up to 10^{-3}M. However, at higher concentrations of ethanol, the yield continues to increase, and, in this system, can eventually attain values which are considerably greater than the maximum that could arise from the hydroxyl radicals resulting solely from the decomposition of water. Over the concentration range considered here, "direct effects," *i.e.*, changes due to the direct absorption of the radiation energy by the solute, cannot amount to more than about 10% even at the highest concentrations employed.

(*b*) The initial yield of hydrogen peroxide, in contrast to that of acetaldehyde, is more or less independent of solute concentration over a relatively wide range (~10^{-3}M to ~1M). Above about M-ethanol, $G(H_2O_2)$ again increases. It is noteworthy that the yield of hydrogen peroxide becomes practically independent of the ethanol concentration when the latter exceeds about 10^{-3}M, *i.e.*, the concentration at which the rate of increase of the yield of acetaldehyde changes markedly.

(*c*) The effect of pH on the yields of aldehyde is more pronounced in the more concentrated ethanol solutions. Between 10^{-4}M and 10^{-1}M, the acetaldehyde yield is more or less the same at pH 1·2 as at pH 5·5. However, in acid solutions, at concentrations above 10^{-1}M, G(acetaldehyde) becomes increasingly greater than the corresponding value at pH 5·5. Using ^{60}Co γ-rays, Swallow [8] has also reported a concentration-dependence of the yields of acetaldehyde. In some preliminary experiments with ^{60}Co γ-radiation,[8] we have shown that

[8] Collyns, Scholes, and Weiss, unpublished experiments.

the dependence of the yields of aldehyde and of hydrogen peroxide on ethanol concentration is essentially similar to that observed with *X*-rays. In addition, the yields of these products (at pH 5·5) are very nearly the same for 200 kv *X*-rays and γ-radiation.

Experiments in the Absence of Oxygen.—Determination of the yield–dose plots for the formation of acetaldehyde, hydrogen, and hydrogen peroxide in 10^{-2}M-ethanol solutions irradiated in the absence of oxygen at pH 1·2 and pH 5·5 shows that at both these pH's the yields of acetaldehyde and of hydrogen are proportional to the dose.[4] In acid solutions, hydrogen peroxide appears to be formed initially in a yield corresponding to $G \simeq 0{\cdot}6$. Under neutral conditions, however, practically no hydrogen peroxide could be detected, owing presumably to the efficient secondary decomposition of this substance.

The variation of the initial yields of aldehyde and hydrogen with pH over the pH range 1—7 is given in Fig. 6. The yields of both these products fall off markedly with increasing pH.

In ethanol solutions, irradiated in the absence of oxygen, butane-2 : 3-diol was also formed. The presence of this diol was established by oxidation by periodic acid. Included in Fig. 6

TABLE 2. *Dependence of the yield on concentration of ethanol in solutions irradiated with* X*-rays* (200 kv) *in vacuo.* (pH = 1·2. *Total dose* = $4{\cdot}29 \times 10^{-6}$ ev/***N*** *per ml.*).

Ethanol concn. (mole/l.)	$3{\cdot}4 \times 10^{-2}$	$1{\cdot}7 \times 10^{-3}$	$1{\cdot}7 \times 10^{-4}$
Yield of acetaldehyde (G)	1·90	1·40	0·70
Yield of butane-2 : 3-diol (G)	1·65	1·15	0·08

are some values for the yields of butane-2 : 3-diol (dose = $3{\cdot}15 \times 10^{-6}$ ev/***N*** per ml.) in solutions irradiated at various pH's; in contrast to the other radiation products, production of butane-2 : 3-diol is not greatly influenced by pH.

The effect of solute concentration on the yields of aldehyde and butane-2 : 3-diol in solutions irradiated *in vacuo* at pH 1·2 is shown in Table 2. Here, also, the yields increase with increasing solute concentration. The yields of the diol fall off rather more rapidly with decreasing ethanol concentration than do those of acetaldehyde.

DISCUSSION

It is generally assumed that dehydrogenation of ethanol by OH radicals takes place at the α-carbon atom, according to :

$$CH_3{\cdot}CH_2{\cdot}OH + OH \longrightarrow CH_3{\cdot}\dot{C}H(OH) + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

In the present work, the observation that butane-2 : 3-diol can be produced by irradiation supports this view. The nature of the radiation products from aqueous ethanol suggests, in fact, that dehydrogenation at the α-position is the only significant chemical primary process which occurs in this system.

In the presence of molecular oxygen, the process $H_2O \rightsquigarrow H + OH$ can be followed by process $H + O_2 \longrightarrow HO_2{\cdot}$, and process (1) by :

$$CH_3{\cdot}\dot{C}H{\cdot}OH + O_2 \longrightarrow CH_3{\cdot}\overset{O_2{\cdot}}{\underset{|}{C}}H{\cdot}OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Hence, under these conditions, we are dealing predominantly with reactions involving peroxy-radicals, and, in the light of the experimental results, the following possibilities may be considered :

$$CH_3{\cdot}\overset{O_2{\cdot}}{\underset{|}{C}}H{\cdot}OH + HO_2 \longrightarrow CH_3{\cdot}CHO + H_2O_2 + O_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$CH_3{\cdot}\overset{O_2{\cdot}}{\underset{|}{C}}H{\cdot}OH + O_2^- \xrightarrow{H^+} CH_3{\cdot}\overset{O_2H}{\underset{|}{C}}H{\cdot}OH + O_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$HO_2 \rightleftharpoons H^+ + O_2^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

$$2CH_3{\cdot}\overset{O_2{\cdot}}{\underset{|}{C}}H{\cdot}OH \longrightarrow CH_3{\cdot}\overset{O_2H}{\underset{|}{C}}H{\cdot}OH + CH_3{\cdot}CHO + O_2 \quad . \quad . \quad . \quad . \quad . \quad (6a)$$

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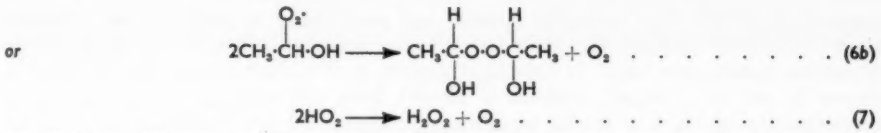

or $2CH_3\cdot\dot{C}H\cdot OH \longrightarrow CH_3\cdot C(OH)\cdot O\cdot O\cdot C(OH)\cdot CH_3 + O_2$ . . . . . (6b)

$2HO_2 \longrightarrow H_2O_2 + O_2$ . . . . . (7)

Interactions between organic peroxy-radicals to form acetic acid, or to form alkoxy-radicals which may then dismutate, can be eliminated since no acetic acid was detectable and, from the results, it follows that no oxygen is used by processes other than those leading to hydrogen peroxide.

Rieche [9] found that in aqueous systems, 1-hydroxyethyl hydroperoxide tends to go over into the di-1-hydroxyethyl peroxide. Kooijman and Ghijsen [10] confirmed this and found that, under these conditions, formation of the peroxide is favoured by a factor of about ten. If, therefore, the hydroperoxide is a product of irradiation it should be converted to a large extent into the peroxide. From some experiments with aqueous solutions of 1-hydroxyethyl hydroperoxide prepared by Rieche's method [9] we have concluded that, if the organic hydroperoxide and peroxide are present at all in the irradiated ethanol solutions, they would be determined as hydrogen peroxide and acetaldehyde by the analytical methods used; from the experimental results, therefore, we are unable to distinguish between reaction (3) on the one hand and reactions (4) and/or (6) on the other.

Wieland and Wingler [11] have studied the behaviour of bishydroxymethyl peroxide in aqueous solution and found that, with titanium sulphate, the yellow colour was formed only after slight warming. This appeared to provide an opportunity for testing whether any organic peroxide was present in irradiated methanol solutions. An aqueous solution of methanol (10^{-2}M) was saturated with oxygen and irradiated with a total dose of $5{\cdot}4 \times 10^{-6}$ ev/**N** per ml. Two aliquot parts were then treated with the titanium reagent, and one of these was warmed. Identical optical densities were observed, presumably indicating the absence of bishydroxymethyl peroxide. If one assumes that the mechanisms of the radiation-induced oxidation of methanol and of ethanol are similar, one may conclude that acetaldehyde is probably formed from ethanol according to reaction (3). However, for a given number of HO_2 and RO_2 radicals, the overall stoicheiometry in terms of hydrogen peroxide and acetaldehyde is the same whether these radicals react according to reaction (3) or according to reactions (4) and/or (6) and (7).

One of the most important quantitative observations in the presence of oxygen is that the yields of hydrogen peroxide are almost independent of ethanol concentration over a wide range (cf. Figs. 4 and 5) and can maintain a relatively high value down to concentrations at which the yields of acetaldehyde are rather low, *i.e.*, when presumably not all of the available OH radicals are reacting with the solute. These findings are incompatible with a mechanism consisting of the primary actions on water followed by the sequence of reactions $H + O_2 \longrightarrow HO_2$, (1), (2), (3), and (7). The additional amounts of hydrogen peroxide which are required to satisfy the observed stoicheiometry, particularly at the lower ethanol concentrations, can only be accounted for if we assume that a certain amount of this substance is formed more or less directly from OH radicals. It has often been suggested that there is a direct recombination of OH radicals to give hydrogen peroxide. However, as has been pointed out,[12] there is strong evidence against such a reaction in the gaseous state, where, according to Bonhoeffer and Pearson,[13] the interaction proceeds according to $2OH \longrightarrow H_2O + O$. A possible explanation of the predominance of this reaction may be that a relatively high activation energy is necessary for the recombination of OH radicals owing to dipolar repulsion.[12] However, in the

[9] Rieche, *Ber.*, 1931, **64**, 2328.
[10] Kooijman and Ghijsen, *Rec. Trav. chim.*, 1947, **66**, 205.
[11] Wieland and Wingler, *Annalen*, 1923, **431**, 301.
[12] Weiss, *Trans. Faraday Soc.*, 1940, **36**, 856.
[13] Bonhoeffer and Pearson, *Z. phys. Chem.*, 1931, *B*, **14**, 1.

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presence of certain other molecular species, and particularly in solutions, the situation might be different and recombinative formation of hydrogen peroxide may be catalysed by various molecules or ions. It appears, therefore, that in solutions one has to include a process in which hydrogen peroxide is formed from OH radicals. This may occur predominantly within the tracks or clusters produced by the radiation. It may be necessary, therefore, to differentiate between OH radicals capable of entering into such a process and those which diffuse into the bulk of the solution or which are formed outside the tracks—hereafter called " readily available OH radicals "—*i.e.*, they can react more readily with the solute than the OH radicals in the densely populated clusters.

Increase in the solute concentration will gradually suppress the reaction :

$$HO_2 + OH \longrightarrow H_2O + O_2 \quad \ldots\ldots\ldots \quad (8)$$

On this basis, it would seem that, at ethanol concentrations above about 10^{-3}M, when the hydrogen peroxide yields begin to flatten out (cf. Figs. 4 and 5), most of these " readily available OH radicals," have been used up by the solute. Thereafter, increasing the solute concentration increases the extent of reaction with the solute [eqn. (1)] compared to the recombination to give hydrogen peroxide. According to the experimental results, the number of such " readily available OH radicals " corresponds to a value of $G = 2$, *i.e.*, corresponding to the yield of acetaldehyde at the point where the curve for the yield of hydrogen peroxide flattens out.

The dependence of the yield of acetaldehyde on temperature (Fig. 2) could be accounted for on the basis of reaction (1) and interaction of OH radicals to form hydrogen peroxide by OH recombination. Increase of reaction (1) at the expense of the latter process would result if rise in temperature influenced (i) the rate of diffusion of the OH radicals from the tracks or (ii) the relative rates of reaction (1) and of the recombination process. In either case, the yield of hydrogen peroxide could remain practically unaltered, as observed experimentally. In terms of activation energies, the observed temperature coefficient could be interpreted as a difference of the order of 0·5—1 kcal. mole^{-1}, a value which would be compatible with each of the above alternatives.

Also of interest is the observation that, at the break-points in aerated solutions, the yields of hydrogen peroxide are slightly higher than would be expected from the amounts of dissolved oxygen present. It may be assumed that the reaction $2H_2O \longrightarrow H_2 + H_2O_2$ would contribute to the yield of hydrogen peroxide to the extent of $G \sim 0{\cdot}6$, this being the value of $G(H_2)$ found for 200 kv *X*-rays. The remaining difference, $G = 1{\cdot}2 - 0{\cdot}6 = 0{\cdot}6$, would be explained if some hydrogen peroxide is also formed by a recombination process from OH radicals.

Another point to consider is the higher yield of peroxide in acid solutions (cf. Fig. 3). The increase between pH 4 and pH 1 amounts to $G \simeq 0{\cdot}6$. This may be regarded as a greater net decomposition of water under acid conditions and can be expressed in terms of an additional overall process :

$$2H_2O \longrightarrow 2H + H_2O_2 \quad \ldots\ldots\ldots \quad (A)$$

which is similar to that known as the " E reaction." [14] Process (A) differs from the " E reaction " in that it must be assumed that the decomposition of water which, in acid solution, leads to hydrogen peroxide according to process (A), does not occur at all in neutral solution; in the case of the " E reaction " it is assumed that the decomposition of water leading to peroxide in acid solution leads, in neutral solution, to OH radicals.

From the point of view of a unified mechanism, it is preferable to regard process A as also resulting primarily from decomposition of water into H and OH; if there is an increased opportunity for interactions of the OH radicals to form hydrogen peroxide, the

$$H + OH \longrightarrow H_2O \quad \ldots\ldots\ldots \quad (9)$$

back-reactions (8) and (9) will be inhibited and this will manifest itself in an increased net decomposition of the water. In acid solutions, process A could be mediated by hydrogen

[14] Allen, *Radiation Res.*, 1954, **1**, 85; Hart, *J. Amer. Chem. Soc.*, 1954, **76**, 4198.

ions, inasmuch as the H_2O^+ ion, which is related to the OH radical by the equilibrium,[15]

$$H_2O^+ \rightleftharpoons OH + H^+ \quad . . . . . (10)$$

could react according to :

$$H_2O^+ + OH \longrightarrow H_3O_2^+ \quad . . . . . (11)$$

$$H_3O_2^+ \rightleftharpoons H_2O_2 + H^+ \quad . . . . . (12)$$

and thus lead to the formation of hydrogen peroxide.

The OH radicals which are utilised in this way may not become available to the solute until relatively high concentrations of the latter are reached; this may explain, at least in part, the greater yields of aldehyde in acid solutions when the concentration of ethanol exceeds about 10^{-1}M. A G value of 0·6 being taken for the reaction $2H_2O \longrightarrow H_2 + H_2O_2$, then at pH ~1 it would follow that $G(OH) = G(H) = 3{\cdot}55$, and at pH >4, $G(OH) = G(H) = 2{\cdot}90$. We thus obtain a more or less complete picture of the processes in ethanol solutions up to between 10^{-2} and 10^{-1}M. At higher concentrations, however, processes other than those involving OH radicals begin to take place. Among these we must consider :

(*a*) Reactions of the solute with hydrogen atoms when the concentration of the former is sufficiently high to compete with oxygen in the process $H + O_2' \longrightarrow HO_2\cdot$. In this case, dehydrogenation of ethanol by hydrogen atoms,

$$CH_3\cdot CH_2\cdot OH + H \longrightarrow CH_3\cdot \dot{C}H\cdot OH + H_2 \quad . . . . . (13)$$

will increase the yield of aldehyde but not influence that of hydrogen peroxide since both the H atoms and the organic radicals ($CH_3\cdot\dot{C}H\cdot OH$) lead to equivalent amounts of hydrogen peroxide *via* reactions $H + O_2 \longrightarrow HO_2\cdot$ plus (3) and (6) + (7) respectively.

(*b*) Electronic excitation of the ethanol molecules by the slow electrons produced by the ionising radiations.[16]

(*c*) Chemical changes due to the direct absorption of the radiation by the ethanol. Such a process could result in an increased yield of hydrogen peroxide as well as of acetaldehyde.

In solutions irradiated in the absence of oxygen we can account for the general qualitative and quantitative features if, in addition to reactions (1) and (13), we have the following processes :

$$\left.\begin{aligned} 2CH_3\cdot\dot{C}H\cdot OH &\longrightarrow CH_3\cdot CH(OH)\cdot CH(OH)\cdot CH_3 \\ CH_3\cdot\dot{C}H\cdot OH + OH &\longrightarrow CH_3\cdot CHO + H_2O \\ CH_3\cdot\dot{C}H\cdot OH + H &\longrightarrow CH_3\cdot CH_2\cdot OH \\ H + H^+ &\rightleftharpoons H_2^+ \end{aligned}\right\} \quad . . . . . (14)$$

$$\left.\begin{aligned} CH_3\cdot CH_2\cdot OH + H_2^+ &\longrightarrow CH_3\cdot\dot{C}H\cdot OH + H_2 + H^+ \\ CH_3\cdot\dot{C}H\cdot OH + H_2^+ &\longrightarrow CH_3\cdot CHO + H_2 + H^+ \\ H_2^+ + H &\longrightarrow H_2 + H^+ \\ 2H &\longrightarrow H_2 \end{aligned}\right\} \quad . . . . . (15)$$

Reactions involving the H_2^+ radical-ion, formed as shown above, will be more predominant at low pH; in this way, we can account for a pH-dependence of all the yields (cf. Fig. 6).

It may be pointed out that if, under vacuum conditions, reaction (16) occurred, this would also lead to higher yields of hydrogen. However, some studies of the effects of X-rays on deaerated solutions of ethanol containing methylene-blue [17] strongly suggest that this reaction does not take place and that the alcohol is dehydrogenated by hydrogen atoms as shown above. In these circumstances, we have also excluded the ordinary dismutation process between two $CH_3\cdot\dot{C}H\cdot OH$ radicals (leading to acetaldehyde and alcohol).

$$CH_3\cdot CH_2\cdot OH + CH_3\cdot\dot{C}H\cdot OH \longrightarrow HO\cdot CHMe\cdot CHMe\cdot OH + H \quad . . . . (16)$$

[15] Weiss, *Experientia*, 1956, **12**, 280.
[16] Weiss, *Nature*, 1954, **174**, 78; *J. Chim. phys.*, 1955, **52**, 40.
[17] Hayon, Scholes, and Weiss, *J.*, 1957, 301.

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In the irradiations of the more strongly acid solutions *in vacuo*, the yields of molecular hydrogen correspond to a radical yield of $G(H) = 3{\cdot}6$, in good agreement with the value derived from the corresponding experiments in the presence of oxygen.

In the absence of oxygen, there appears to be no evidence for any hydrogen peroxide formation from OH radicals; it is, therefore, suggestive that such a process may be catalysed by molecular oxygen.

It is known that many free radicals show a great tendency to combine with molecular oxygen. It would, therefore, be reasonable to assume that this may happen also in the case of OH radicals [18] possibly according to the equilibrium process, *viz.*,

$$OH + O_2 \rightleftharpoons HO_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

and the HO_3 could then react according to :

$$HO_3 + OH \longrightarrow H_2O_2 + O_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

thus leading to hydrogen peroxide. Some support for the assumption of HO_3 comes from the existence of the corresponding metal compounds ($Me^{I}O_3$) which have been investigated by various authors.[19]

Both reactions (10)—(12), and (17) and (18), would provide a mechanism for the interaction of OH radicals to give hydrogen peroxide which would be free from the objections discussed above. As an alternative to the above suggestions for the additional yields of hydrogen peroxide in certain conditions, it is not impossible that in these conditions a back-reaction between hydrogen peroxide (or one of its precursors) and hydrogen atoms may be inhibited.

The adoption of these suggestions regarding the mechanisms of the above processes must rest on a more detailed study of the initial yields of hydrogen peroxide *in vacuo* and perhaps also on a rather more precise determination of the yields of butane-2 : 3-diol under various conditions.

In solutions irradiated *in vacuo*, interaction between OH radicals by reaction (10) could still result in oxidation of ethanol by means of the oxygen atoms, *viz.*,

$$CH_3{\cdot}CH_2{\cdot}OH + O \longrightarrow CH_3{\cdot}\dot{C}H{\cdot}OH + OH$$

followed by reaction (14). However, the formation of acetaldehyde in this way is already covered by reactions (1) and (14) of our suggested mechanism for evacuated solutions.

Experimental

Irradiations.—The solutions were irradiated with *X*-rays (200 kv, 15 ma) as previously described.[7] Dose rates were determined by the ferrous sulphate dosimeter, $G(Fe^{3+})$ being taken [20] as 15·5, and, in these experiments, were of the order of $0{\cdot}9—2{\cdot}7 \times 10^{-7}$ ev/N per ml. per min.

The Pyrex vessel for irradiation at constant temperature is shown in Fig. 7. Water from a large constant-temperature reservoir was pumped through the outer jacket (*A*) both before and throughout the irradiation. By measurements of the oxygen contents of the aerated ethanol solutions at different temperatures, by Winkler's method,[21] it was found that equilibrium between the gas phase and the solution was established sufficiently rapidly by this procedure.

Solutions were prepared in triply distilled water, ordinary distilled water being redistilled in an all-glass still from alkaline permanganate and then from phosphoric acid. The final distillate had a pH between 5·3 and 5·6. Where it was necessary to adjust the pH of the solutions, sulphuric acid was used for pH <4·0, Sørensen buffer (KH_2PO_4–Na_2HPO_4) for pH 4·5—pH 7·5, and sodium hydroxide for pH >10·0. " AnalaR " ethanol was used without further purification. Other materials were, when possible, of " AnalaR " grade.

[18] Stein, *J. Chim. phys.*, 1955, **52**, 634.
[19] Kasarnowsky, Nikolskii, and Abletsova, *Doklady Akad. Nauk S.S.S.R.*, 1949, **64**, 960; Whale and Kleinberg, *J. Amer. Chem. Soc.*, 1951, **73**, 79.
[20] Farmer, Rigg, and Weiss, *J.*, 1955, 582.
[21] Winkler, *Ber.*, 1888, **21**, 2843.

A strict procedure was adhered to when cleaning the irradiation vessels. After being washed with " Teepol " the vessel was rinsed several times, washed with cleaning mixture (either sulphuric acid–nitric acid or ethanol–nitric acid), and rinsed with triply distilled water.

Irradiations were carried out in the presence of air or of oxygen (1 atm.), the solution being saturated by passage of oxygen for about 15 min. For experiments in the absence of oxygen, the evacuation was carried out as follows: the solution was pumped out by means of a two-stage " Hyvac " oil-pump, shaken for a few minutes, and next morning, evacuated with a mercury-diffusion pump. The amounts of dissolved oxygen in the solutions were then less than $0{\cdot}5 \times 10^{-6}$ mole/ml.

Detection and Determination of Acetaldehyde.—The aldehyde was isolated from the irradiated solutions as its 2 : 4-dinitrophenylhydrazone, identified by paper-chromatography, the solvent being light petroleum–methanol.[22] This 2 : 4-dinitrophenylhydrazone was determined by Johnson and Scholes's method.[23] Barker and Summerson's method [24] could not be used in the irradiated solutions owing to interference by ethanol and hydrogen peroxide.

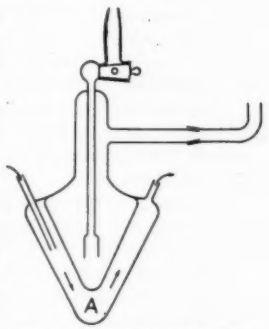

FIG. 7. *Constant-temperature reaction vessel.*

Determination of Hydrogen Peroxide.—This was estimated with titanium sulphate; [25] no interference was observed by acetaldehyde in the quantities formed in the irradiated solutions. Identical results were obtained by Hochenadel's iodide method.[26]

Determination of Butane-2 : 3-diol.—Experiments with the pure substance showed that it could be readily detected and determined by the formation of acetaldehyde on treatment with periodic acid. The procedure was as follows: to a 100-ml. sample in a distillation apparatus were added, from a dropping funnel, 100 ml. of periodic acid (0·01M-potassium periodate in 0·15M-sulphuric acid) followed by 5 ml. of concentrated sulphuric acid and 15 ml. of distilled water. About 80 ml. of the mixture were then distilled over into a flask (containing about 10 ml. of distilled water) cooled in ice–water. The distillate was then made up to 100 ml., and the acetaldehyde content determined.

For irradiated solutions, hydrogen peroxide in the presence of alcohol interfered in the determination of butane-2 : 3-diol, giving additional amounts of acetaldehyde equivalent to about 25% of the peroxide present. Correction was made for this by the addition of comparable amounts of hydrogen peroxide to the blank solutions. The butanediol estimations has an estimated accuracy of $\pm 7\%$.

Gas Analysis.—The gas-analysis apparatus was similar to that described by Stein and Weiss.[27] After irradiation *in vacuo*, the gases were pumped from the vessel, through a liquid-air trap, by means of a semiautomatic Töpler pump, and hydrogen was determined manometrically after combustion in the presence of excess of oxygen.

Tests for the Presence of Other Possible Reaction Products in Solutions irradiated in the Presence of Oxygen.—(a) *Acetic acid.* A suitable method for this substance appeared to be that of Hutchens and Kass.[28] Since the lower limit of this method is about 2×10^{-6} moles/ml., it was necessary to concentrate the irradiated solutions before applying the test. This was carried out as follows:

To eliminate acetaldehyde (which might be oxidised to acetic acid by hydrogen peroxide) 20 ml. of a solution of 2 : 4-dinitrophenylhydrazine (0·25% w/v in 30% perchloric acid) were added to 100 ml. of the irradiated solution (10^{-2}M-ethanol, total dose $= 3 \times 10^{-6}$ ev/N per ml.). The bulk of the solution was then distilled *in vacuo* into strong alkali. The distillate was taken to dryness, the residue acidified with phosphoric acid, and the solution distilled into a few ml. of strong alkali. This process was repeated once more and the final distillate (~3 ml.) was tested with the lanthanum nitrate reagent. A negative result was obtained, even after

[22] Meigh, *Nature*, 1952, **170**, 579.
[23] Johnson and Scholes, *Analyst*, 1954, **79**, 217.
[24] Barker and Summerson, *J. Biol. Chem.*, 1941, **138**, 535.
[25] Eisenberg, *Ind. Eng. Chem. Analyt.*, 1943, **15**, 327.
[26] Hochenadel, *J. Phys. Chem.*, 1952, **56**, 587.
[27] Stein and Weiss, *J.*, 1949, **3245**.
[28] Hutchens and Kass, *J. Biol. Chem.*, 1949, **177**, 571.

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combining the products of three irradiations, and it was therefore concluded that, if acetic acid was formed at all, the G value must be less than 0·3.

This conclusion was substantiated by measurements of the " titratable acidity " of the blank and irradiated solutions. Small amounts of titratable acid could be detected, but only after relatively high doses. For instance, after a total dose of $8{\cdot}5 \times 10^{-6}$ ev/N per ml., the G values of acetic acid in 3×10^{-2}M- and $6{\cdot}8 \times 10^{-1}$M-ethanol solutions were 0·26 and 0·44 respectively. This strongly suggests that acetic acid is not a primary radiation product but can arise by some secondary oxidation processes.

(b) *Ethylene glycol.* This was tested for by a combination of the methods reported by Tompsett and Smith [29] and by O'Dea and Gibbons.[30] This involved oxidation to formaldehyde with periodic acid, removal of the aldehyde by distillation, and colorimetric determination with chromotropic acid. No glycol could be detected in 10^{-2}M-ethanol solutions which had been irradiated with a total dose of 6×10^{-6} ev/N per ml.

(c) *Glycolaldehyde.* This forms an osazone with 2 : 4-dinitrophenylhydrazine, which gives a strong blue colour on addition of alkali; benzene was used to extract the osazone from the aqueous solution. In spite of the fact that this solvent extracts a relatively large quantity of the unchanged reagent as well as acetaldehyde 2 : 4-dinitrophenylhydrazone, it was possible to detect added osazone in quantities down to about 10^{-8} mole/ml. When the irradiated ethanol solutions (10^{-2}M; total dose = $8{\cdot}5 \times 10^{-6}$ ev/N per ml.) were treated in this way, a negative result was obtained.

(d) *Ethyl hydroperoxide and diethyl peroxide.* Neither of these substances reacts with the titanium reagent. The former, however can oxidise iodide to iodine and ferrous thiocyanate to ferric thiocyanate;[31] the latter can oxidise ferrous thiocyanate but not iodide.

Since identical yields of peroxide were obtained by using these three methods, it was concluded that no ethyl hydroperoxide or diethyl peroxide was formed on irradiation.

(e) *Peracetic acid.* That this compound was not produced was indicated by the absence of any significant amounts of " titratable acid " after irradiation.

(f) *Ethyl acetate.* This can be detected in relatively low quantities (10^{-4}M) by the method developed by Lipmann and Tuttle [32] and adapted by Lieberman :[33] 25 ml. of the irradiated solution were treated with 20 ml. of alkaline hydroxylamine reagent, and the whole set aside for 10 min. The mixture was then acidified with hydrochloric acid, and ferric chloride added. There was no absorption at 540 mμ, a wavelength characteristic of the ferric–acetohydroxamic acid which is formed from ethyl acetate under these conditions.

Experiments with 1-Hydroxyethyl Hydroperoxide.—This hydroperoxide was prepared as described by Rieche [9] as follows : 50 ml. of hydrogen peroxide (30% w/v) were extracted three times with 40 ml. of ether, and the combined extracts dried (Na_2SO_4). The ethereal solution contained ~0·1 mole of hydrogen peroxide, and an equimolar quantity of freshly prepared acetaldehyde was added. This mixture was stored for two days in a refrigerator. For analytical purposes the ether was distilled off *in vacuo*, and the 1-hydroxyethyl hydroperoxide weighed.

An aqueous solution containing $0{\cdot}35 \times 10^{-7}$ mole per ml. of the hydroperoxide was made up. The amounts of hydrogen peroxide as determined by titanium sulphate, and of acetaldehyde as found by treatment with 2 : 4-dinitrophenylhydrazine, were 0·34 and $0{\cdot}32 \times 10^{-7}$ mole per ml. respectively. With these analytical methods, therefore, the total hydroperoxide could be accounted for in terms of hydrogen peroxide and acetaldehyde.

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[29] Tompsett and Smith, *Analyst*, 1953, **78**, 209.
[30] O'Dea and Gibbons, *Biochem. J.*, 1953, **55**, 580.
[31] Egerton, Everett, Minkoff, Rudrakanchana, and Salooja, *Analyt. Chim. Acta*, 1954, **10**, 422.
[32] Lipmann and Tuttle, *J. Biol. Chem.*, 1943, **159**, 21.
[33] Lieberman, *Arch. Biochem. Biophys.*, 1954, **51**, 350.

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259. *The Ionisation of Dinitrogen Tetroxide in Nitric Acid. Evidence from Measurements of Infrared Spectra and Magnetic Susceptibilities.*

By D. J. Millen and D. Watson.

The infrared spectra of solutions of dinitrogen tetroxide in anhydrous nitric acid have been found to contain lines belonging to nitrosonium and nitrate ions. Lines due to non-ionised dinitrogen tetroxide appeared with increasing intensity as the concentration of the solutions was increased. None of the lines expected for non-ionised nitrogen dioxide was observed. Intensity measurements have been interpreted to show that in dilute solutions one nitrate ion is formed per solute molecule, consistent with the ionisation :

$$N_2O_4 \longrightarrow NO^+ + NO_3^-$$

The magnetic susceptibilities of these solutions have been measured and interpreted to confirm the conclusion, reached from the infrared-spectral study, that the extent of the dissociation :

$$N_2O_4 \longrightarrow 2NO_2$$

is very small compared with that of the ionic dissociation.

It has been concluded from Raman-spectral studies that dinitrogen tetroxide in dilute solution in nitric acid is dissociated partly homolytically, but mainly heterolytically :

$$2NO_2 \rightleftharpoons N_2O_4 \rightleftharpoons NO^+ + NO_3^-$$

The frequency associated with the nitrosonium ion, obtained for these solutions, is at about 2240 cm.$^{-1}$ and is considerably below the usual value of 2300 cm.$^{-1}$. It was suggested that it is unlikely that the low value is due to a solvent effect, for two main reasons. First, for solutions of nitrosonium hydrogen sulphate and perchlorate in nitric acid peaks were obtained at 2300 cm.$^{-1}$. Secondly, it was shown that for solutions of dinitrogen tetroxide in nitric acid, the frequency is restored to its normal value by the addition of small quantities of sulphuric acid.

Lynn, Mason, and Corcoran [2] have measured optical densities of solutions of dinitrogen tetroxide in nitric acid, with and without addition of potassium nitrate. Their conclusion that the fraction of solute which is ionised in dilute solution (up to 0·06 molal-dinitrogen tetroxide) is 0·7 $\pm$ 0·3, shows that the extent of ionisation is considerable, but allows the interpretations that the extent of the homolytic dissociation is comparable or negligible.

One of the main objects of the present work was to obtain information about the relative importance of the heterolytic and homolytic dissociations.

Infrared-spectral Evidence.—The infrared spectrum of a 7 molal *-solution of dinitrogen tetroxide in anhydrous nitric acid is compared with that of the solvent in Fig. 1. Frequencies observed are listed in Table 1, the first column listing those frequencies which belong to the solvent and the second those which are not so attributable. The remaining columns list those infrared active fundamentals, which fall in the region concerned, for the species NO_3^-,[3] N_2O_4,[4] NO_2,[5] and NO^+.

The strong line at 2220 cm.$^{-1}$ is attributed to the nitrosonium ion. The unusually low value for the frequency confirms the results of Goulden and Millen; the value obtained here is even lower than the values obtained by Raman spectroscopy, but the solutions

* Concentrations of solutions are given as stoicheiometric molality of dinitrogen tetroxide unless otherwise stated.

[1] Goulden and Millen, *J.*, 1950, 2620.
[2] Lynn, Mason, and Corcoran, *J. Phys. Chem.*, 1955, **59**, 238.
[3] Williams and Decherd, *J. Amer. Chem. Soc.*, 1939, **61**, 1382.
[4] Perkins and Wilson, *Phys. Rev.*, 1952, **85**, 755.
[5] Moore, *J. Opt. Soc. Amer.*, 1953, **43**, 1045.

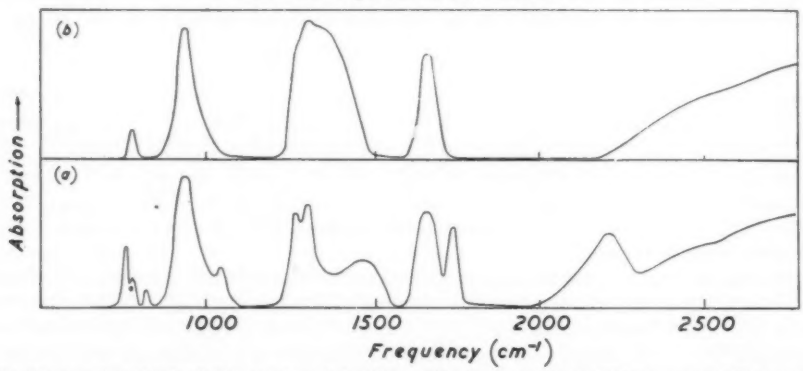
used in the latter case were more dilute. The presence of nitrate ion is clearly indicated by the strong appearance of the allowed fundamentals, 830 and 1350 cm.$^{-1}$. The line at 1050 cm.$^{-1}$ is also attributed to the nitrate ion, for it was also found in the infrared spectra

TABLE 1. *Frequencies (cm.$^{-1}$).*

Belonging to the solvent	Not belonging to the solvent	NO_3^-	N_2O_4	NO_2	NO^+	Belonging to the solvent	Not belonging to the solvent	NO_3^-	N_2O_4	NO_2	NO^+
—	—	675	684	—	—	1300	—	—	—	—	—
—	750	—	748	750	—	—	—	—	—	1323	—
770	—	—	—	—	—	—	1400	1350	—	—	—
—	830	830	—	—	—	—	—	—	—	1616	—
930	—	—	—	—	—	1664	—	—	—	—	—
—	1050	—	—	—	—	—	1750	—	1747	—	—
—	1260	—	1260	—	—	—	2220	—	—	—	2300

of solutions of potassium nitrate in nitric acid. This frequency corresponds to the totally symmetric stretching vibration, being well known in the Raman spectrum of the nitrate ion, and is presumably allowed in the infrared spectrum of the solution because of an

FIG. 1. *Comparison of the infrared spectrum of a 7 molal-solution of* (a) *dinitrogen tetroxide in nitric acid with the spectrum of* (b) *the solvent.*



(The diagram is not intended to compare intensities of bands, since the conditions were not the same for all the bands.)

effective lowering of symmetry by solvation. The remaining lines, apart from those of the solvent, are attributed to undissociated dinitrogen tetroxide, for they correspond well in frequency and relative intensity to the fundamental frequencies in this region, reported by Perkins and Wilson.[4] The infrared spectrum does not provide evidence of non-ionised nitrogen dioxide in these solutions. It may be that the fundamental frequency at about 750 cm.$^{-1}$ is masked by a line due to the tetroxide, and that at about 1320 cm.$^{-1}$ is obscured by a broad band due to the overlap of lines due to nitric acid and nitrate ion, but the fundamental frequency at 1620 cm.$^{-1}$ should serve to identify non-ionised nitrogen dioxide.

The spectra of solutions of other concentrations in the range 2·5 to 12 molal, are similar to that in Fig. 1, except that the dinitrogen tetroxide bands become more prominent at the higher concentrations. An attempt was made to estimate quantitatively, by means of intensity measurements, the fraction of solute which is ionised in these solutions. The optical densities of the line at 830 cm.$^{-1}$ due to nitrate ion and that at 770 cm.$^{-1}$ due to nitric acid were measured for a number of solutions of potassium nitrate in nitric acid. A calibration curve of the ratio of the optical densities of these two lines was used to

estimate the concentration of nitrate ion in solutions of dinitrogen tetroxide from the ratio of the optical densities of the same two lines in the spectra of these solutions. The results are shown in Fig. 2, which is a plot, as a function of concentration, of the number of solute molecules required to produce one nitrate ion. The results become inaccurate at the higher concentrations because the intensity measurements are made difficult by the appearance of a dinitrogen tetroxide band at 750 cm.$^{-1}$, and also because of possible loss of solute by evaporation. However, it is clear that as the solutions become more dilute, one nitrate ion is produced per solute molecule. This is consistent with the ionisations :

$$N_2O_4 \rightleftharpoons NO^+ + NO_3^-$$
$$N_2O_4 + HNO_3 \rightleftharpoons NO_3^- + HN_2O_4^+$$

The method cannot distinguish between these ionisations, since $HN_2O_4^+$ is analytically equivalent to solvated NO^+. A protonated dinitrogen tetroxide molecule is excluded as the source of the strong line at 2220 cm.$^{-1}$, since this value is too high to be one of the ion's fundamental frequencies.

The results, as can be seen from Fig. 2, confirm the conclusion reached from a study of Raman spectra, that for solutions up to about 1 molal of stoicheiometric dinitrogen

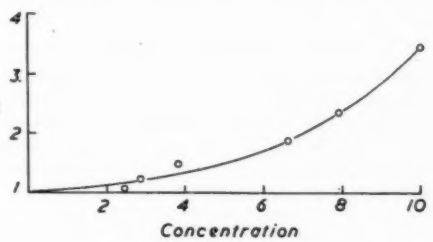


FIG. 2. *The number* (n) *of dinitrogen tetroxide molecules required to produce one nitrate ion, plotted as a function of concentration* (*stoicheiometric molality*).

tetroxide, the concentration of undissociated tetroxide is small. It is clear too, from the infrared spectra, that solutions up to this concentration do not contain appreciable quantities of nitrogen dioxide, for, first, lines belonging to this molecule were not observed and, secondly, nearly all of the solute is accounted for by the above ionisation.

The dependence of the frequency of the nitrosonium ion on its environment has been further examined. A 5 molal-solution of dinitrogen tetroxide was examined at a number of temperatures between 20° and −40°. The frequency was found to increase slightly from 2235 cm.$^{-1}$ to 2264 cm.$^{-1}$, with fall in temperature. Finally, the sample was frozen at −185°. The infrared spectrum of the crystals contained a strong line at 2255 cm.$^{-1}$, showing that the ionisation occurs in the solid phase as well as in solution. The nitrosonium ion frequency was measured in the infrared spectra of solid nitrosonium hydrogen sulphate $NO^+HSO_4^-$ and in nitrosonium tetrachloroaluminate NO^+AlCl^{4-}. The values obtained were 2275 cm.$^{-1}$ and 2238 cm.$^{-1}$, respectively.

Among the solutions examined was an 8% w/w solution of nitrosonium hydrogen sulphate in nitric acid. This gave a value of about 2315 cm.$^{-1}$ for the frequency of the nitrosonium ion. The addition of small quantities of sulphuric acid to solutions of dinitrogen tetroxide in nitric acid led to an increase in the frequency of the nitrosonium ion. These results confirm qualitatively the variations in frequency observed in the Raman spectra of these solutions. The present work establishes that the low value of the frequency in the spectra of solutions of dinitrogen tetroxide is not due to an intervention of molecular nitrogen dioxide.

Evidence from Magnetic Susceptibilities of Solutions.—The magnetic susceptibilities of several solutions of dinitrogen tetroxide in nitric acid are recorded in Table 2, together

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with the susceptibilities of some solutions of potassium nitrate in nitric acid. All the solutions of both solutes are diamagnetic, the susceptibility passing through a maximum in each case. The initial rise in susceptibility presumably reflects the repression by nitrate ion of the self-dissociation of the solvent. The similarity of the susceptibilities for the two solutions shows that the solutions of dinitrogen tetroxide do not contain appreciable amounts of

TABLE 2. *Magnetic susceptibilities* (s) *of solutions of dinitrogen tetroxide and potassium nitrate in nitric acid at* 18°.

N_2O_4, molality	*s* per g.	N_2O_4, molality	*s* per g.	KNO_3, molality	*s* per g.
0·815	−0·317	3·511	−0·310	1·041	−0·334
1·173	−0·316	3·672	−0·317	1·571	−0·344
1·455	−0·323	5·827	−0·305	2·338	−0·355
2·107	−0·322	6·813	−0·294	3·740	−0·325
2·614	−0·332			4·587	−0·335
				HNO_3	−0·325

a paramagnetic species. If the assumption is made that the difference between the susceptibilities of the two solutions is due to a paramagnetic contribution from nitrogen dioxide, with one unpaired electron, then it can be calculated that the concentration of nitrogen dioxide does not exceed 0·02 molal in the most concentrated solution examined.

Experimental.—The infrared spectra were recorded with a Hilger D 209 spectrometer, used as a single-beam instrument. For the spectra of solutions in nitric acid, a single drop of the sample was placed between two silver chloride windows and a suitable cell thickness was obtained by clamping the windows together. For the spectra at low temperatures an apparatus similar to that described by Wagner and Hornig [6] was used. In this apparatus the cell is surrounded by a jacket which can be evacuated, or filled with dry nitrogen or air. The cell itself may then be cooled to the appropriate temperature by a freezing mixture, solid carbon dioxide, or liquid nitrogen. A suitable film of nitrosonium hydrogen sulphate was prepared by melting a sample and then allowing it to crystallise. The spectrum of nitrosonium tetrachloroaluminate was observed by using a mull with liquid paraffin.

Magnetic susceptibility measurements were made by the Gouy method, and are probably correct to within about 2%.

Nitric acid was prepared by distillation, at a pressure of about 2 cm. of mercury, from a mixture of 1 part of commercial 97% nitric acid and 3 parts of sulphuric acid. The distillate was collected in a trap cooled in liquid nitrogen. The product was redistilled until a colourless product was obtained.

Dinitrogen tetroxide was prepared by heating " AnalaR " lead nitrate. The product was dried by distillation over phosphoric oxide in a stream of oxygen.

Nitrosonium hydrogen sulphate was prepared by passing sulphur dioxide through nitric acid, and the tetrachloroaluminate by passing nitrosyl chloride through aluminium chloride dissolved in liquid sulphur dioxide.

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[*Received, October 9th,* 1956.]

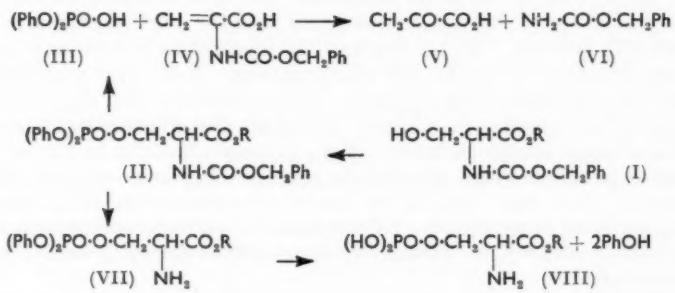
[6] Wagner and Hornig, *J. Chem. Phys.*, 1950, **18**, 298.

260. *Synthesis of Some Phosphorylated Amino-hydroxy-acids and Derived Peptides related to the Phosphoproteins.*

By G. Riley, J. H. Turnbull, and W. Wilson.

Diphenyl phosphorochloridate has been used to prepare a number of (di-*O*-phenylphospho)serine derivatives. In attempts to remove protecting phenyl groups, the action of alkali on these products has been studied; *N*-acylated compounds readily afford diphenyl hydrogen phosphate and acrylic acid derivatives by a β-elimination process. However, compounds having a free serine amino-group can be hydrolysed by alkali to phenol (2 mols.) and *O*-phosphorylserine derivatives. These reactions have been used in syntheses of phosphoserine, phosphothreonine, phosphoserylglycine, and phosphoserylglutamic acid. Hydrogenolysis also has been successfully used for removing phenyl groups in this series.

Several phosphorylated peptides have been obtained by partial hydrolysis of natural phosphoproteins, and similarly from certain enzymes (*e.g.*, cholinesterases and chymotrypsin) which have been inhibited by di*iso*propyl phosphorofluoridate.[1] By further hydrolysis of these peptides the following simple fragments have been isolated: serine dihydrogen phosphate ester (phosphoserine);[2] threonine dihydrogen phosphate ester (phosphothreonine);[3] phosphoserylglycine;[4] and phosphoserylglutamic acid.[5] If it is assumed[4,6] that no rearrangement occurs during hydrolysis, these phosphate units should exist in the parent phosphoproteins. The present work (for a preliminary account see ref. 7) concerns the development of general methods of synthesising such units. Diphenyl phosphorochloridate has been used throughout as the phosphorylating agent. Earlier workers in this field tended to use more drastic reagents.[8]



The synthesis of DL-phosphoserine was first investigated. *N*-Benzyloxycarbonyl-DL-serine ethyl ester (I; R = Et), with diphenyl phosphorochloridate in pyridine, afforded

[1] Perlmann, *Adv. Protein Chem.*, 1955, **10**, 1; Ågren and Glomset, *Acta Chem. Scand.*, 1953, **7**, 1071; Flavin, *J. Biol. Chem.*, 1954, **210**, 771; Oosterbaan, Kunst, and Cohen, *Biochim. Biophys. Acta*, 1955, **16**, 299.

[2] de Verdier, *Acta Chem. Scand.*, 1954, **8**, 1302; Ågren, de Verdier, and Glomset, *Acta Chem. Scand.* 1951, **5**, 324; 1954, **8**, 1570; Lipmann and Levene, *J. Biol. Chem.*, 1932, **98**, 109; Lipmann, *Biochem. Z.*, 1933, **262**, 3; Schaffer, May, and Summerson, *J. Biol. Chem.*, 1954, **206**, 201; 1953, **202**, 67.

[3] de Verdier, *Acta Chem. Scand.*, 1953, **7**, 196.

[4] Schaffer, Harshman, and Engle, *J. Biol. Chem.*, 1955, **214**, 799.

[5] Levene and Hill, *ibid.*, 1933, **101**, 711; Posternak and Pollaczek, *Helv. Chim. Acta*, 1941, **24**, 921.

[6] Plapinger and Wagner-Jauregg, *J. Amer. Chem. Soc.*, 1953, **75**, 5757.

[7] Riley, Turnbull, and Wilson, 14th Internat. Congr. Pure Appl. Chem., Zurich, 1955, Handbook, p. 133.

[8] Plimmer, *Biochem. J.*, 1941, **35**, 461; Levene and Schormüller, *J. Biol. Chem.*, 1934, **106**, 595; Posternak and Grafl, *Helv. Chim. Acta*, 1945, **28**, 1258.

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the diphenyl phosphate ester (II; R = Et). In such reactions it was necessary to protect the carboxyl group by esterification.[9] Attempts to remove the phenyl groups from the ester (II) by alkaline hydrolysis failed: a β-elimination reaction (cf. refs. 10) ensued yielding diphenyl hydrogen phosphate (III) and α-*N*-benzyloxycarbonylaminoacrylic acid (IV). The structure of the latter was established by the existence of intense light absorption at 241 mμ (ε 5300), and by its hydrolysis to benzyl carbamate (VI) and pyruvic acid (V). Alternatively the benzyloxycarbonyl group was removed from the diphenyl phosphate (II) by treatment with hydrogen bromide in acetic acid.[11] The resulting amino-ester (VII; R = Et) (obtained as the crystalline hydrobromide) has little tendency to undergo the elimination; careful treatment with alkali at room temperature rapidly yielded phenol (2 mols.) and DL-phosphoserine (VIII; R = H) isolated by way of the lead or barium salt. At higher temperatures (*ca.* 90°) the yield of phosphoserine decreases, and appreciable amounts of diphenyl hydrogen phosphate and pyruvic acid are formed indicating that β-elimination is again favoured. These reactions are readily followed by measuring the light absorption of the phenol produced;[12] diphenyl hydrogen phosphate is easily recognised by the isolation of the *cyclo*hexylammonium salt. The resistance of the amino-ester (VII) to β-elimination in cold alkaline solution is attributed to the inductive effect of the α-amino-group which would hinder expulsion of the α-proton. Alkaline hydrolysis of other diphenyl phosphates (*e.g.*, cholesteryl diphenyl phosphate) has been shown to yield alkali-stable phenyl hydrogen phosphates.[12] The production of the dihydrogen phosphate in the alkaline hydrolysis of the diphenyl phosphate (VII) and the extreme rapidity with which phenol is formed in both aqueous and aqueous-alcoholic media suggest that the formation of cyclic intermediates involving the amino- or carboxyl group may be facilitating removal of *both* phenyl groups.[13]

Reactions similar to the foregoing have been used for making L-phosphoserine and DL-phosphothreonine. The method has also been successfully extended to the synthesis of certain phosphorylated peptides, notably DL-phosphoserylglycine. Attempts to prepare the latter from the diphenyl phosphate ester of *N*-benzyloxycarbonyl-DL-serine ethyl ester by way of the azide were unsuccessful, since the ester underwent β-elimination on treatment with (strongly basic) hydrazine. It appeared to be necessary to start with a serylglycine derivative as in the following synthesis. *N*-Benzyloxycarbonyl-DL-serylglycine ethyl ester, prepared from the azide, reacted smoothly with diphenyl phosphorochloridate in pyridine, yielding the diphenyl phosphate characterised by its readily undergoing β-elimination in alkaline solution. With hydrogen bromide in glacial acetic acid, however, this diphenyl phosphate afforded the corresponding amino-derivative from which DL-phosphoserylglycine was obtained by careful treatment with alkali, two mols. of phenol being produced concurrently. L-Phosphoseryl-L-glutamic acid, previously isolated from casein hydrolysates,[1,5] was similarly synthesised from diethyl *N*-benzyloxycarbonyl-L-seryl-L-glutamate.

The use of alkaline hydrolysis to remove phenyl groups limits the foregoing method to the synthesis of peptides in which the phosphoserine or phosphothreonine amino-groups are free, for with *N*-substituted derivatives β-elimination predominates. Removal of phenyl groups by catalytic hydrogenolysis should permit the synthesis of peptides containing phosphoserine or phosphothreonine residues in any position. This alternative has now been used for the synthesis of phosphoserine. In preliminary experiments hydrogenolysis of the diphenyl phosphate ester of *N*-benzyloxycarbonyl-DL-serine ethyl ester (II; R = Et) resulted in the removal of the benzyloxycarbonyl and the phenyl groups, affording

[9] Cf. Friedkin and Lehninger, *J. Biol. Chem.*, 1947, **169**, 183.
[10] Linstead, Owen, and Webb, *J.*, 1953, 1211; Riley, Turnbull, and Wilson, *Chem. and Ind.*, 1953, 1181; Brown, Fried, and Todd, *J.*, 1955, 2206.
[11] Ben-Ishai and Berger, *J. Org. Chem.*, 1952, **17**, 1564.
[12] Montgomery, Turnbull, and Wilson, *J.*, 1956, 4603.
[13] Cf. Chanley and Feageson, *J. Amer. Chem. Soc.*, 1955, **77**, 4002; Moffatt and Khorana, *ibid.*, 1956, **78**, 883.

DL-phosphoserine ethyl ester (VIII; R = Et). Similarly, hydrogenolysis of the corresponding benzyl ester [14,15] (II; R = CH_2Ph) yielded DL-phosphoserine, the ester benzyl group being removed simultaneously. The hydrogenolysis method is being studied further.

The possibility of O ⟶ N migration [6,14] of phosphate groups was borne in mind but no evidence for this was found. Electrophoretic and potentiometric titrations appear to favour the dihydrogen phosphate ester formulation.

Experimental

The expression ε^* is used for the apparent molecular extinction coefficient of the solute after it has undergone some transformation, *e.g.*, hydrolysis.

N-Benzyloxycarbonyl-DL-serine.—Benzyl chloroformate (8·8 g.) was added to a solution of DL-serine (4·0 g.) in saturated aqueous sodium hydrogen carbonate (80 c.c.). The mixture was stirred vigorously for 2 hr. at 25°, excess of chloroformate removed by extraction with ether, and the aqueous solution acidified with concentrated hydrochloric acid. The oily product slowly deposited crystals (8·0 g.), m. p. 122—125°, which recrystallised from ethyl acetate in needles, m. p. 125—126° (Found: C, 55·2; H, 5·1; N, 5·7. Calc. for $C_{11}H_{13}O_5N$: C, 55·2; H, 5·4; N, 5·8%). Bergmann and Zervas [16] give m. p. 125°; the use of sodium hydrogen carbonate is a substantial improvement on the procedure of these authors.

N-Benzyloxycarbonyl-DL-threonine.—The *product* (0·75 g.) obtained from benzyl chloroformate (0·95 g.) and DL-threonine (0·5 g.) according to the foregoing method was isolated by extraction with ethyl acetate and recrystallised therefrom in needles, m. p. 74—75° (Found: C, 56·6; H, 5·8. $C_{12}H_{15}O_5N$ requires C, 56·9; H, 5·9%).

N-Benzyloxycarbonyl-DL-serine Ethyl Ester.—Benzyl chloroformate (4·5 g.) was added to a vigorously stirred mixture of DL-serine ethyl ester hydrochloride (4·0 g.) and saturated sodium hydrogen carbonate solution (70 c.c.) at 20°. After 2 hr. extraction with ether afforded the *ester* (4·5 g., 64%), b. p. 150—156°/0·01 mm. (Found: C, 58·0; H, 6·1; N, 5·2. $C_{13}H_{17}O_5N$ requires C, 58·4; H, 6·4; N, 5·2%).

N-Benzyloxycarbonyl-DL-(di-O-phenylphospho)serine Ethyl Ester.—*N*-Benzyloxycarbonyl-DL-serine ethyl ester (8·0 g.), dry pyridine (100 c.c.), and diphenyl phosphorochloridate (9·0 g.) were mixed. After being kept at 0° for 12 hr., the mixture was diluted with chloroform (100 c.c.) and washed with dilute hydrochloric acid and with water. Evaporation and recrystallisation from ether–light petroleum gave the *diphenyl phosphate* as needles (13·7 g., 85%), m. p. 40—41°, $\lambda_{max.}$ 261 mμ (ε 787 in EtOH) (Found: N, 2·7; P, 6·1. $C_{25}H_{26}O_8NP$ requires N, 2·8; P, 6·2%). The compound, on treatment with aqueous-ethanolic alkali, rapidly developed an absorption band at 244 mμ (ε^* 5000) which remained after acidification. This band is due to the formation of *N*-α-benzyloxycarbonylaminoacrylic acid (see following experiment) by β-elimination; diphenyl hydrogen phosphate which is also formed absorbs only weakly ($\lambda_{max.}$ 261 mμ; ε 1000).

α-N-*Benzyloxycarbonylaminoacrylic Acid.*—The foregoing diphenyl phosphate (0·2 g.) was dissolved in acetone (5 c.c.), and 2N-sodium hydroxide (2 c.c.) added. After 10 min., the acetone was removed in a vacuum and the residue carefully acidified to Congo-red by concentrated hydrochloric acid. Recrystallisation of the solid precipitate (50 mg.; m. p. 93—96°) from water gave α-N-*benzyloxycarbonylaminoacrylic acid*, m. p. 106—108°, $\lambda_{max.}$ 241 mμ (ε 5300 in H_2O) (Found: C, 59·5; H, 4·9; N, 6·3. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0; N, 6·3%). Addition of *cyclo*hexylamine to the original mother-liquors afforded *cyclo*hexylammonium diphenyl phosphate, m. p. and mixed m. p. 198°. The above acrylic acid derivative was stable to 2N-sodium hydroxide; 5N-sodium hydroxide converted it into benzyl carbamate, m. p. 88—89°. Refluxing it with dilute hydrochloric acid gave benzyl carbamate and pyruvic acid (2 : 4-dinitrophenylhydrazone, m. p. 217°).

DL-(*Di*-O-*phenylphospho*)*serine Ethyl Ester Hydrobromide.*—*N*-Benzyloxycarbonyl-DL-(di-*O*-phenylphospho)serine ethyl ester (6·0 g.) and a saturated solution of hydrogen bromide in glacial acetic acid (15 c.c.) were mixed at 0° and dry ether (500 c.c.) was added. After several

[14] Jones and Lipkin, *J. Amer. Chem. Soc.*, 1956, **78**, 2408.
[15] Si-Oh Li and Eakin, *ibid.*, 1955, **77**, 1866; Miller and Waelsch, *ibid.*, 1952, **74**, 1092; Baer and Maurukas, *J. Biol. Chem.*, 1955, **212**, 25.
[16] Bergmann and Zervas, *Ber.*, 1932, **65**, 1192; Doub and Vandenbelt, *J. Amer. Chem. Soc.*, 1947, **69**, 2714.

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hours at 0°, the ether layer was decanted, the residual syrup triturated with aqueous methanol, and the dry solid product (5 g.; m. p. 46—52°) recrystallised from ethyl acetate–ether. The *hydrobromide* (4·8 g.) formed needles, m. p. 63—64° (Found: C, 45·9; H, 4·9; N, 3·1. $C_{17}H_{21}O_6NPBr$ requires C, 45·8; H, 4·7; N, 3·1%). Light absorption max. at 260 mμ (ε 510 in H_2O). In a similar experiment with hydrogen chloride in glacial acetic acid, the corresponding *hydrochloride* (10%), m. p. 99—100°, was obtained (Found: N, 3·2. $C_{17}H_{21}O_6NPCl$ requires N, 3·5%).

Action of Alkali on DL-(*Di*-O-*phenylphospho*)*serine Ethyl Ester Hydrobromide.*—(*a*) The hydrobromide was dissolved in aqueous alkali at a suitable temperature and concentration; the amount of phenol liberated was measured at appropriate times by measuring the ultraviolet light absorption of aliquot parts of the solution at 234 mμ (phenoxide ion absorption) or, after acidification, at 270 mμ (undissociated phenol absorption).[16] Optimum conditions for the hydrolysis were with N-sodium hydroxide at 22° for 5 min.; 2 mols. of phenol were liberated.

(*b*) The hydrobromide (0·2 g.) was mixed with 2N-sodium hydroxide (5 c.c.); the oily free base rapidly dissolved on shaking. After 30 min. at 20°, acidification and addition of bromine water gave 2 : 4 : 6-tribromophenol (0·2 g.; m. p. 94—95°). Addition of *cyclo*hexylamine to the mother-liquors gave no precipitate, indicating the absence of significant amounts of diphenyl hydrogen phosphate.

(*c*) The hydrobromide (0·2 g.) was heated at 90° with N-sodium hydroxide. After 5 min., the solution was acidified and bromine water added to precipitate 2 : 4 : 6-tribromophenol (0·1 g.; m. p. 93—94°). Addition of *cyclo*hexylamine to the filtrate gave *cyclo*hexylammonium diphenyl phosphate (70 mg.; m. p. 198—199°). Treatment of the acidified mother-liquors with 2 : 4-dinitrophenylhydrazine gave pyruvic acid 2 : 4-dinitrophenylhydrazone, m. p. 211—213°.

DL-*Phosphoserine.*—(*a*) DL-(Di-*O*-phenylphospho)serine ethyl ester hydrobromide (1·0 g.) was shaken vigorously with N-sodium hydroxide (10 c.c.) until a clear solution was obtained. After a further 30 min. acetic acid was added to pH 4. Phenol was removed by ether-extraction, and the aqueous solution concentrated to a small volume; saturated lead acetate solution was added, and the lead salt of phosphoserine was collected, suspended in water, and decomposed with hydrogen sulphide. The solution was evaporated and ethanolic ether added. The precipitate [100 mg.; m. p. 145—150° (decomp.)] was dissolved in water and reprecipitated with ethanol–ether, to give DL-phosphoserine (75 mg., 18%) as small prisms, m. p. 163—164° (decomp.) (Found: C, 19·4; H, 4·6; N, 7·1. Calc. for $C_3H_8O_6NP$: C, 19·5; H, 4·4; N, 7·6%). Plimmer [5] gives m. p. 165—166° (decomp.), and Plapinger and Wagner-Jauregg [6] m. p. 166—167° (decomp.)

(*b*) DL-(Di-*O*-phenylphospho)serine ethyl ester hydrobromide (0·5 g.) and N-sodium hydroxide (5 c.c.) were set aside for 30 min., then percolated through Amberlite IR-120 resin (H^+ form), and the effluent extracted with ether and made alkaline (phenolphthalein) by aqueous barium hydroxide. The filtrate was evaporated, ethanol added, the precipitated barium salt (0·28 g.) dissolved in water, and percolated through Amberlite IR-120 resin (H^+ form), and phosphoserine [70 mg., 33%; m. p. 162—163° (decomp.)] isolated from the effluent by evaporation and precipitation with ethanol–ether.

N-*Benzyloxycarbonyl*-L-(*di*-O-*phenylphospho*)*serine Ethyl Ester.*—L-Serine {m. p. 219—220° (decomp.), $[\alpha]_D$ −6·2° (*c* 2·3 in H_2O)} with absolute ethanol and hydrogen chloride gave the ethyl ester hydrochloride, m. p. 130—131°, $[\alpha]_D$ −4·8° (*c* 2·1 in H_2O), which was converted into the *N*-benzyloxycarbonyl derivative, then treated with diphenyl phosphorochloridate in pyridine, as in the case of the DL-isomer, affording the *diphenyl phosphate ester*, m. p. 39—40°, $[\alpha]_D^{20}$ −1° (*c* 2·9 in EtOH) (Found: C, 60·0; H, 5·4; N, 2·9. $C_{25}H_{26}O_8NP$ requires C, 60·1; H, 5·2; N, 2·8%), $\lambda_{max.}$ 261 mμ (ε 760 in EtOH); treatment with 0·5N-sodium hydroxide in 50% ethanol at 20° for 30 min. produced a strong absorption band (238 mμ, ε* 5450, unchanged on cautious acidification), indicating the formation of *N*-benzyloxycarbonylaminoacrylic acid.

L-(*Di*-O-*phenylphospho*)*serine Ethyl Ester Hydrobromide.*—Prepared from the foregoing diphenyl phosphate (1·5 g.) and hydrogen bromide in glacial acetic acid, this *hydrobromide* was obtained as needles (1·1 g.), m. p. 67—68° (Found: N, 3·1; P, 6·5. $C_{17}H_{21}O_6NPBr$ requires N, 3·1; P, 7·0%), $\lambda_{max.}$ 260 mμ (ε 500 in EtOH). Treatment with 0·02N-aqueous sodium hydroxide at 20° for 30 min. liberated two mols. of phenol by hydrolysis.

L-*Phosphoserine.*—The above hydrobromide (0·25 g.) was dissolved in methanol, N-sodium hydroxide (2 c.c.) added, and the mixture left for 30 min. at 20°. A barium salt was isolated,

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by the foregoing procedure for DL-phosphoserine. The barium salt (100 mg.), $[\alpha]_D^{19}$ +5·5° (*c* 3·6 in HCl), gave free L-phosphoserine (32% yield), m. p. 175—176° (decomp.), $[\alpha]_D^{19}$ +12° (calc. from Ba salt; *c* 3·6 in N-HCl) (Found: N, 7·5; P, 16·3. Calc. for $C_3H_8O_6NP$: N, 7·6; P, 16·7%). Ågren *et al.*[2] give m. p. 167° (decomp.), $[\alpha]_D^{23}$ +7·2° (*c* 4·2 in H_2O). Levene and Schormüller [8] give $[\alpha]_D^{25}$ +16·3° (calc. from Ba salt; *c* 6·0 in 10% HCl), and Lipmann and Levene [2] $[\alpha]_D^{25}$ +17·3° (calc. from Ba salt; *c* 1·7 in 10% HCl).

N-*Benzyloxycarbonyl*-DL-(*di*-O-*phenylphospho*)*threonine Ethyl Ester*.—DL-Threonine ethyl ester hydrochloride (m. p. 116—117°) was converted into crude *N*-benzyloxycarbonyl-DL-threonine ethyl ester in 82% yield. This (1·6 g.) with diphenyl phosphorochloridate (1·6 g.) in dry pyridine gave the *diphenyl phosphate ester* (1·8 g., 61%), m. p. 56—57° after recrystallisation from ether–light petroleum (Found: N, 3·1; P, 5·8. $C_{26}H_{28}O_8NP$ requires N, 2·7; P, 6·0%), $\lambda_{max.}$ 261 mμ (ε 730 in EtOH). In dilute sodium hydroxide solution it developed characteristic absorption at 231 mμ (ε* 6250).

DL-(*Di*-O-*phenylphospho*)*threonine Ethyl Ester Hydrobromide*.—The foregoing product (1·3 g.) and a saturated solution of hydrogen bromide in glacial acetic acid (3 c.c.) gave, as in the similar reactions already described, the *hydrobromide* (0·4 g., 45%), m. p. 88—89°, $\lambda_{max.}$ 260 mμ (ε 430 in H_2O) (Found: N, 3·0; P, 6·4. $C_{18}H_{23}O_6NPBr$ requires N, 3·0; P, 6·7%). Phenol (2 mols.) was rapidly liberated in 0·1N-sodium hydroxide at 20°.

DL-*Phosphothreonine*.—The above hydrobromide (0·3 g.) with N-sodium hydroxide (3 c.c.) and methanol (3 c.c.) at 20° for 30 min. afforded a crude barium salt (0·15 g.) by the procedure outlined for DL-phosphoserine. The barium salt in water with Amberlite IR-120 resin (H^+ form) yielded DL-phosphothreonine (12 mg., 10%), m. p. 150—152° (decomp.) (Found: N, 6·7. Calc. for $C_4H_{10}O_6NP$: N, 7·0%). Plimmer [8] gives m. p. 169° (decomp.), Plapinger and Wagner-Jauregg [6] give m. p. 184° (decomp.).

N-*Benzyloxycarbonyl*-DL-*serine Hydrazide*.—Crude *N*-benzyloxycarbonyl-DL-serine ethyl ester (4·5 g.), hydrazine hydrate (2·5 c.c.), and absolute ethanol (50 c.c.) were left at 20° for 24 hr. An equal volume of ether was added, and the mixture set aside at 0° for several hr. The precipitate (3·3 g., m. p. 156—157°) was recrystallised from ethanol–ether, yielding the *hydrazide* (3·2 g., 75%) as fine needles, m. p. 162—163° (Found: C, 52·3; H, 6·1; N, 16·0. $C_{11}H_{15}O_4N_3$ requires C, 52·5; H, 6·0; N, 16·5%).

N-*Benzyloxycarbonyl*-L-*serine Hydrazide*.—Prepared from *N*-benzyloxycarbonyl-L-serine ethyl ester (1·9 g.) by the foregoing method, this was obtained as needles (1·4 g.), m. p. 180—181°, from ethanol. Fruton [17] gives m. p. 181°.

N-*Benzyloxycarbonyl*-DL-*threonine Hydrazide*.—This *derivative* was obtained from *N*-benzyloxycarbonyl-DL-threonine ethyl ester as needles, m. p. 171—172° (Found: C, 53·4; H, 6·5; N, 16·0. $C_{12}H_{17}O_4N_3$ requires C, 53·9; H, 6·4; N, 15·7%).

N-*Benzyloxycarbonyl*-DL-*serylglycine Ethyl Ester*.—*N*-Benzyloxycarbonyl-DL-serine hydrazide (3·0 g.) was suspended in water (30 c.c.) and glacial acetic acid (3 c.c.), and concentrated hydrochloric acid (1·0 c.c.) was added. Sodium nitrite (0·5 g.) in water (3 c.c.) was added dropwise at 0°. The azide was extracted into ethyl acetate, washed with water, and dried. Meanwhile, glycine ethyl ester hydrochloride (5·0 g.) was treated with cold saturated potassium carbonate, the free glycine ester isolated with ether, and the ether solution dried, then mixed with the above azide solution. After 24 hr. at 20°, the mixture was washed with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), and evaporated. Light petroleum (b. p. 40—60°) precipitated a solid which was recrystallised from ethyl acetate–light petroleum (b. p. 40—60°), affording the *peptide* (0·4 g., 57%), m. p. 86—87° (Found: C, 55·6; H, 6·3; N, 9·0. $C_{15}H_{20}O_6N_2$ requires C, 55·5; H, 6·2; N, 8·6%).

DL-(*Di*-O-*phenylphospho*)*serylglycine Ethyl Ester Hydrobromide*.—*N*-Benzyloxycarbonyl-DL-serylglycine ethyl ester (1·0 g.) with diphenyl phosphorochloridate in pyridine gave the crude diphenyl phosphate ester (1·6 g.) as an oil ($\lambda_{max.}$ 260 mμ, ε 537). This developed a characteristic absorption band at 236 mμ (ε* 7000) in dilute aqueous-alcoholic sodium hydroxide.

The crude diphenyl phosphate (1·7 g.) with saturated hydrogen bromide in glacial acetic acid gave a salt which, recrystallised from ethanol–ethyl acetate, afforded the *hydrobromide* (0·6 g., 45%), m. p. 129—130° (Found: C, 45·1; H, 4·5; N, 5·5. $C_{19}H_{24}O_7N_2PBr$ requires C, 45·5; H, 4·8; N, 5·6%). The substance, with N-sodium hydroxide at 20°, liberated 2 mols. of phenol in less than 4 min.

[17] Fruton, *J. Biol. Chem.*, 1942, **146**, 463.

DL-*Phosphoserylglycine*.—The above hydrobromide (0·5 g.), methanol (2 c.c.), and N-sodium hydroxide (5 c.c.) were left at 20° for 30 min. The solution was percolated through Amberlite IR-120 resin (H^+ form), extracted with ether, neutralised with barium hydroxide solution, and evaporated below 30°; ethanol was added, the barium salt isolated, dissolved in water, and treated with Amberlite IR-120 (H^+ form), and the solution evaporated and diluted with ethanol. The crystalline product (45 mg., 18%), m. p. 150—154° (decomp.) was DL-phosphoserylglycine (Found: N, 11·5. Calc. for $C_5H_{11}O_7N_2P$: N, 11·6%). Fölsch [18] records m. p. 178°.

Diethyl N-*Benzyloxycarbonyl*-L-(*di*-O-*phenylphospho*)*seryl*-L-*glutamate*.—*N*-Benzyloxycarbonyl-L-serine hydrazide was converted into the azide, which was dissolved in anhydrous ethyl acetate and mixed with ethereal diethyl L-glutamate. After 20 hr., the product was recrystallised from ethyl acetate–light petroleum (b. p. 40—60°), yielding diethyl *N*-benzyloxycarbonyl-L-seryl-L-glutamate (58%; m. p. 81—82°) (Fruton [17] gives m. p. 85—86°). This ester (1·0 g.) with diphenyl phosphorochloridate–pyridine gave the crude diphenyl phosphate ester (1·45 g.) as an oil, $\lambda_{max.}$ 261 mμ (ε 800 in EtOH). With 0·04N-sodium hydroxide in aqueous ethanol at 20° the solution developed a characteristic absorption band at 234 mμ (ε* 8000 after 30 min.).

L-*Phosphoseryl*-L-*glutamic Acid*.—The foregoing crude diphenyl phosphate with hydrogen bromide gave diethyl L-(di-*O*-phenylphospho)seryl-L-glutamate hydrobromide as a syrup, $\lambda_{max.}$ 260 mμ (ε 430). The substance rapidly liberated 2 mols. of phenol in cold 0·1N-aqueous ethanolic sodium hydroxide. The crude hydrobromide with aqueous-methanolic sodium hydroxide gave, after appropriate processing, a barium salt {0·6 g.; $[\alpha]_D^{22}$ −1·3° (*c* 3·12 in N-HCl)} which was converted into L-*phosphoseryl*-L-*glutamic acid* (35 mg.), m. p. 145—147° (Found: N, 8·8. $C_8H_{15}O_9N_2P$ requires N, 8·9%). The brucine salt was obtained as small plates, m. p. 160—162° (Levene and Hill [5] record m. p. 171—172° for the salt).

DL-*Phosphoserine Ethyl Ester*.—*N*-Benzyloxycarbonyl-DL-(di-*O*-phenylphospho)serine ethyl ester (0·585 g.) was shaken in glacial acetic acid (20 c.c.) with platinum oxide (45 mg.) in hydrogen. After 16 hr., the solution gelled; a little water was added and hydrogenation continued for 3 hr. The solution was evaporated to small bulk below 40°; addition of ethanol precipitated the *ester* (0·17 g.), m. p. 170—171° (Found: N, 6·5; OEt, 20·05. $C_5H_{12}O_6NP$ requires N, 6·6; OEt, 21·1%).

DL-*Serine Benzyl Ester Benzenesulphonate*.—Serine (3·6 g.) and commercial hydrated benzenesulphonic acid (5·5 g.) were dissolved in benzyl alcohol (30 c.c.) and dry benzene (20 c.c.). The benzene was slowly distilled off, whilst more benzene (40 c.c.) was dropped in. The solution was cooled, and dry ether added: the solid (11 g.; m. p. 96—100°) was recrystallised three times from acetone–ether, to yield the *benzyl ester benzenesulphonate* (5 g.), m. p. 115—116° (Found: N, 3·9. $C_{16}H_{19}O_6NS$ requires N, 4·0%). A portion of the salt was treated with triethylamine in chloroform, triethylammonium benzenesulphonate filtered off, and the filtrate evaporated and treated with hydrogen chloride in ether. This yielded the benzyl ester hydrochloride, m. p. 154°. The foregoing procedure is a modification of that of Miller and Waelsch.[15]

N-*Benzyloxycarbonyl*-DL-*serine Benzyl Ester*.—The foregoing benzenesulphonate (3·5 g.) was treated with benzyl chloroformate (2·0 g.) and saturated sodium hydrogen carbonate solution (75 c.c.). After vigorous stirring during 1 hr., the product (2·8 g.; m. p. 70—72°) was filtered off. Recrystallisation from ether–light petroleum (b. p. 40—60°) gave the benzyloxycarbonyl derivative (2·3 g.), m. p. 74—75° (cf. Miller *et al.*[15]) (Found: N, 4·5. Calc. for $C_{18}H_{19}O_5N$: N, 4·25%).

N-*Benzyloxycarbonyl*-DL-(*di*-O-*phenylphospho*)*serine Benzyl Ester*.—*N*-Benzyloxycarbonyl-DL-serine benzyl ester (1·6 g.) was treated in pyridine (3 c.c.) with diphenyl phosphorochloridate (1·5 g.) in pyridine (2 c.c.). After 2 hr., ether and water were added, and the ether layer washed with dilute hydrochloric acid. Evaporation of the ether and trituration with light petroleum (b. p. 40—60°) gave a wax. Recrystallisation from ether–light petroleum (b. p. 40—60°) gave the *diphenyl phosphate ester* (2·4 g.), m. p. 49—50° (Found: N, 2·85. $C_{30}H_{28}O_8NP$ requires N, 2·5%), $\lambda_{max.}$ 260 mμ (ε 900 in EtOH). Treatment with 0·01N-aqueous-ethanolic sodium hydroxide at 20° developed a characteristic band at 239 mμ (ε* 5500).

DL-*Phosphoserine*.—The foregoing diphenyl phosphate (0·5 g.) in glacial acetic acid (10 c.c.) with platinum oxide (55 mg.) was shaken in hydrogen for about 7 hr.; a little water was added

[18] Fölsch, *Acta Chem. Scand.*, 1955, **9**, 1039.

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during the reaction to dissolve a gel which formed. The solution was filtered, then concentrated in a vacuum, and absolute ethanol added. The crystalline product (0·15 g.) had m. p. 160—161° (decomp.) (Found: N, 7·4. Calc. for $C_3H_9O_6NP$: N, 7·6%).

Potentiometric Titrations.—DL-Phosphoserine (11 mg.) was dissolved in water (5 c.c.) and titrated with 0·029N-sodium hydroxide. A Marconi pH meter in combination with a glass electrode was employed. The titration curve showed typical inflexions at pH 4·25, 7·75, and 10·4. DL-Phosphoserine ethyl ester, titrated similarly, gave a curve with inflexions at pH 3·8, 6·8, and 9·5.

Paper Electrophoresis.—Electrophoresis was carried out on Whatman No. 3 paper in 0·1M-acetate buffer at pH 4·15 with a current of 30 mA and a gradient of 8 v cm.$^{-1}$. Ninhydrin was used as developer. The following migrations were observed:

Distance (cm.) moved towards:	cathode	anode
Serine	3·4	—
DL-Phosphoserine	—	11·5
DL-Phosphoserine ethyl ester	1·4	—

Grateful acknowledgment is made to Professor M. Stacey, F.R.S., for constant encouragement. We are much indebted to Mr. D. Sutcliffe for the potentiometric and electrophoretic data. One of us (G. R.) thanks the Department of Scientific and Industrial Research for a maintenance grant.

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261. *The Nature of the Co-ordinate Link. Part X.* The Effect of Ligands on the Redox Potentials of Non-ionic Platinous Complexes and the Evidence it gives for the Effect of Dative π-Bonding on the Total Transfer of Charge in Co-ordinate Bonds.*

By STEN AHRLAND and J. CHATT.

The redox potentials of some systems of the type L_2PtCl_4–L_2PtCl_2 have been measured in a mixed aqueous solvent (Table 1). When L = PPr^n_3, the redox potential of the *cis*-isomer system is higher than that of its *trans*-analogue. Our results indicate that both inductive withholding and mesomeric withdrawal of electrons from the metal by the ligand stabilises the lower-valent state of the metal against oxidation. This work, in conjunction with earlier evidence, indicates that with *metals in their usual valency states* and with ligands such as the alkyls of the elements of Groups V and VI, the total electron transfer between ligand and metal is not greatly affected by dative π-bonding; but that the mesomeric release of electrons from the metal to the ligand in dative π-bonding induces an almost compensating inductive release of electrons from the ligand to the metal in the σ-bond. In this way the metal-to-ligand bond is significantly strengthened by double bonding, but its electrical asymmetry is only slightly affected, so that the bond retains the high dipole moment usually associated with co-ordinate bonds.

DURING a study of olefin complexes [1] of platinous chloride it was suggested that the difference between the redox potentials of corresponding *cis*- and *trans*-couples of the type L_2PtCl_4–L_2PtCl_2 in a series of compounds having different uncharged ligands, L, would give some measure of the relative double-bonding tendencies of the uncharged ligands. This conclusion was based on the consideration that in a series of simple analogous redox reactions such as (1) the redox components are uncharged and entropy effects will be roughly constant. Therefore the only important factor which would change in passing

* Part IX, *J.*, 1954, 4403.

[1] Chatt and Duncanson, *J.*, 1953, 2939.

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from one couple, L_2PtCl_4–L_2PtCl_2, to another, L'_2PtCl_4–L'_2PtCl_2, would be the electron affinity of the metal atom, as it is adjusted by the electron affinities of the ligands.

$$L_2PtCl_4 + 2e^- \rightleftharpoons L_2PtCl_2 + 2Cl^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (I)$$

If the ligands tend to withhold or withdraw electrons from the metal atom, it will accept electrons more readily, *i.e.*, it will be more easily reduced, and the lower-valent state will become stabilised against oxidation. Withholding of electrons can occur through poor donation of electrons from ligand to metal in the σ-bond; withdrawal of electrons can occur from the *d*-orbitals of the metal atom in the formation of a dative π-bond.[2] Thus the electron-withholding or -withdrawal may be inductive and mesomeric in character.[3,4] When we consider two corresponding redox systems of *cis*- and *trans*-configurations in which all the ligands are the same, the withholding due to the inductive effect, since it is electrostatic in character, should be nearly equal in both systems. On the other hand, the mesomeric release of electrons from the metal to the ligands will depend on the configuration of the complex. When there are ligands which have strong double-bonding properties in *trans*-positions to each other they compete for electrons from the same *d*-orbitals. Mesomeric withdrawal will then be less than when they are in *cis*-positions where they can withdraw electrons from different *d*-orbitals.[5] Thus the *cis*- should have a greater resistance to oxidation than the *trans*-complex, *i.e.*, the *cis*-redox couple should have the higher potential. Since mesomeric electron withdrawal is the same phenomenon as dative π-bonding in these complexes, the greater the difference between the dative π-bonding tendencies of the ligands, L, and the chloride ion, the greater the difference in redox potentials between the *cis*- and the *trans*-couple. Unfortunately we have not yet been able to obtain suitable corresponding *cis*- and *trans*-couples to use the method to determine the relative double-bonding tendencies of uncharged ligands containing different donor atoms, but the difference between the potentials of the one *cis*- and *trans*-pair of couples which we have been able to examine accords with the above reasoning.

The difficulties in using the method are caused by the following factors.

(1) The platinum complexes are non-ionic and insoluble or very sparingly soluble at 25° in water and in most aqueous organic solvents. The platinic complexes are in general the less soluble and it was very difficult to find a solvent which would dissolve both them and the neutral salt necessary to provide an ionic medium. Aqueous methanol, ethanol, acetone, dioxan, acetic acid, and tetrahydrofurfuryl alcohol all proved useless, and finally aqueous phenol containing 25% of water was used. Tetraethylammonium chloride (0·1M) was used as the neutral salt, because inorganic salts caused the solvent to separate into two phases.

(2) It must be possible to isolate all four complexes of each set. The redox electrode requires 1—5 days to reach equilibrium with the solutions, presumably because the redox components are covalent and uncharged. The complexes must remain unchanged in solution for that length of time. Many platinic complexes of the type *cis*-$[L_2PtCl_4]$ isomerise spontaneously in solution, and from our experience of them only the amine and the tertiary phosphine complexes are likely to remain essentially unchanged sufficiently long. A number of amine complexes were tried, but all proved too insoluble for measurements except that of 4-*n*-pentylpyridine (pepy), and here we did not obtain the *cis*-platinous isomer.

The cell used was:

$$+Au \;\Big|\; \begin{array}{l} L_2PtCl_4\ (C_{IV}),\ L_2PtCl_2\ (C_{II}) \\ NEt_4Cl\ (0{\cdot}1M) \\ \text{Solvent: PhOH 75\%, } H_2O\ 25\%. \end{array} \;\Big|\; Ag,\ AgCl-$$

[2] Chatt, *Nature*, 1950, **165**, 637.
[3] Chatt, Duncanson, and Venanzi, *J.*, 1955, 4456; *Chem. and Ind.*, 1955, 749.
[4] *Idem*, *J.*, 1955, 4461.
[5] See Chatt and Wilkins, *J.*, 1952, 4300, and previous references quoted therein.

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The potentials measured are redox potentials of the complex compound system because the e.m.f., E, of the cell obeyed Nernst's law, $E = E_0 + 29{\cdot}58 \log C_{IV}/C_{II}$ (at 25°; E in mv), when the concentrations of the platinum complexes, C_{IV} and C_{II}, were changed. Here E_0 includes the constant potential of the Ag,AgCl electrode. The cell was sensitive to light and so all measurements were made in the dark. The values of E_0 for the complexes examined are listed in Table 1.

TABLE 1. *Difference* (ΔE_0) *between the redox potentials* (mv) *of the systems* L_2PtCl_4–L_2PtCl_2.

	(*a*)		(*b*)		(*c*)		(*d*)
L	PPr^n_3		PPr^n_3		Pr^n_2S		pepy
Configuration	*cis*		*trans*		*trans*		*trans*
E_0	367		349		441		475
ΔE_0		18		92		34	

The values of E_0 have no absolute significance, but the differences should be almost equal to the differences between the standard redox potentials of the couples concerned: to be exactly equal, the ratio of the activity coefficients of the platinic to the platinous complexes should be the same in all systems examined. This must be almost so since measurements were made in practically the same medium throughout, and also because the redox components are themselves uncharged molecules whose activity coefficients should be very close to unity, whatever the medium. Nevertheless, the total e.m.f. of the cell should be very dependent on the activity of the chloride ion. This activity may be changed by altering either the solvent or the neutral salt used to provide the chloride ion. Thus the couple (*b*) in Table 1 had $E_0 = 400$ mv when tetramethyl- was used instead of tetraethyl-ammonium chloride (0·1M).

The sign convention used in this paper is such that the more positive is the redox potential, the more resistant to oxidation is the Pt(II) complex. From the E_0 values which we have measured it appears that Pt(II) is stabilised by electron withdrawal into the ligand, whether the withdrawl is mesomeric in the dative π-bond, or inductive in the σ-bond. In general, the two effects should operate together and our observations give distinct evidence of both of them.

The difference (18 mv) between the redox potentials of *cis*-$(Pr^n_3P)_2PtCl_4$–*cis*-$(Pr^n_3P)_2PtCl_2$ and the corresponding *trans*-couple (*a* and *b* in Table 1) must be caused by the difference in mesomeric electron withdrawal as explained above (p. 1380). The differences between the redox potentials of the *trans*-systems (*b*, *c*, and *d* in Table 1) must be caused by inductive withholding of electrons in the σ-ligand-to-metal bond. This is evident because mesomeric electron withdrawal would increase in the order of donor atoms N < S < P, so raising the redox potentials in that order.[4] Actually the potentials increase in the reverse order, which is the order of increasing electronegativities of the donor atoms.

These very few experiments indicate a simple general scheme for the influence of ligands on the redox potentials of covalent or inner-orbital complexes. Electron-withholding or -withdrawal by the ligand, whether inductive or mesomeric, increases the electron affinity of the metal, and so stabilises the lower relative to the higher oxidation state. Ewens [6] has already observed the same correlation between the redox potentials of substituted trisphenanthroline-ferrous complexes and the electron-attracting or -releasing properties of the substituents. The more electron-withdrawing the substituent the higher the redox potential.

Nevertheless, the scheme appears to be at variance with the common observation that the most electronegative co-ordinating atoms fluorine and oxygen bring out the highest valency states of elements with which they are combined. This apparent anomaly arises

[6] Ewens, *Nature*, 1945, **155**, 398; see Brandt, Dwyer, and Gyarfas, *Chem. Rev.*, 1954, **54**, 1000, for further references.

because in this work we are comparing the relative oxidisabilities of our complexes using the same oxidant in every case, and the only variant is the ligand, L.

The reactions may each be written :

$$L_2PtCl_2 + 2Cl^- \rightleftharpoons L_2PtCl_4 + 2e^-$$

or

$$L_2PtCl_2 + 2Cl \rightleftharpoons L_2PtCl_4$$

In saying that the higher-valent states of metals are stabilised, *e.g.*, by fluorine, the comparison is actually between such reactions as

$$PtF_4^{2-} + 2F \rightleftharpoons PtF_6^{2-}$$

and

$$PtCl_4^{2-} + 2Cl \rightleftharpoons PtCl_6^{2-}$$

In these examples the oxidants are different as well as the ligands attached to the platinum atom. Thus the comparison is not between the relative oxidisability of PtF_4^{2-} and $PtCl_4^{2-}$ but between some combination of this and the relative oxidising powers of fluorine and chlorine. In other words, fluorine stabilises metals in high-valent states because the element is a good oxidising agent (*i.e.*, is a good electron-acceptor), and it does not necessarily follow that fluoro-complexes with metals in low-valent states are easily oxidised (*i.e.*, that they give up electrons readily).

In this connection it may be worth noting that the redox potentials of the systems $[Fe(CN)_5NH_3]^{2-}$–$[Fe(CN)_5NH_3]^{3-}$ and $[Fe(CN)_5H_2O]^{2-}$–$[Fe(CN)_5H_2O]^{3-}$ have been estimated, although not with certainty, under comparable conditions.[7] The redox potential appears to be raised from 374 to 491 mv (*i.e.*, the lower-valent state is stabilised) when nitrogen as donor atom is replaced by the more electronegative oxygen atom.

In comparing a series of complexes of a particular metal with a number of donor molecules, covering a great range in electronegativity, it must not be overlooked that sometimes a sudden discontinuity in properties occurs because of a complete change in hybridisation of the metal atom. In this paper we are considering only the more subtle changes produced by the ligands in inner-orbital complexes and not complete changes of that type.

It was shown previously [4] that the uncharged organic ligands may be placed in a series—amines, sulphides, selenides, tellurides, arsines, phosphines, stibines, phosphites, and olefins—such that certain properties of their $PtCl_2$ complexes change regularly. From the amines to the arsines the properties were determined largely by the electronegativities of the donor atoms; beyond the arsines the mesomeric effects of the ligands became significant, increasing to ethylene. It appears that the redox potentials of the couples *trans*-L_2PtCl_4–*trans*-L_2PtCl_2 also fit that general pattern. The potentials which we have measured for amine, sulphide, and phosphine complexes are determined mainly by the electronegativities of the donor atom, but we know that $[C_2H_4PtCl_3]^-$, in which there is strong dative π-bonding between the metal and olefin, is virtually incapable of being oxidised. On the other hand, $[NH_3PtCl_3]^-$ can be oxidised readily.[1,8] It thus seems that if we could obtain the measurements to permit us to draw a graph of the standard redox potentials ($E°$) of the systems *trans*-L_2PtCl_4–*trans*-L_2PtCl_2 against donor atoms in the sequence of ligands, L, corresponding to that on page 4465 of ref. 4 it would appear somewhat as in the Figure.

The Effect of Dative π-Bonding on the Polarity of Co-ordinate Bonds.—Since the redox potentials give us some direct relative measure of the electron affinities of the platinum atoms in the complexes, these results, although few, are of considerable significance for the indication they give of the relative importance of electron-donation in the σ-bond and back-donation in the π-bond. We now have definite evidence, mainly from work previously reported, that dative π-bonding is of very minor importance so far as electron transfer in the ligand–metal bond is concerned, in the case of all the common donor atoms N, S, Se, Te, As, P, and Sb in their alkyl derivatives.

[7] Davidson, *J. Amer. Chem. Soc.*, 1928, **50**, 2622.
[8] Hel'man and Ryabchikov, *Compt. rend. Acad. Sci. U.R.S.S.*, 1941, **33**, 462.

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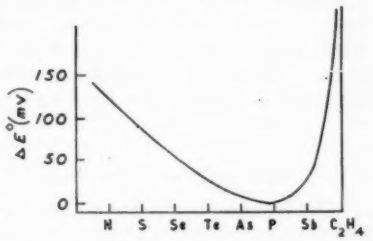
The evidence is: (1) The close correlation of the N–H stretching frequencies of the complexes of the type *trans*-[L,amine $PtCl_2$] with the electronegativities of the donor atoms in L, and the smooth relation between the frequency and intensity of the absorption bands, where L is an alkyl derivative of the above donor atoms.[4]

(2) The high dipole moments (~11 D) of such complexes as *cis*-[$(MR_3)_2PtCl_2$], where M = P, As, or Sb.[5,9] Since the Pt–Cl bond moment is probably of the order 2 D,[10] the $PtCl_2$ part of the molecule will contribute about 3 D to the total moment, and so the M–Pt bond moment must be of the order 5·5 D. When we compare this with the moment [11] (7·03 D) of the molecule PMe_3,BCl_3, where dative π-bonding cannot occur and the BCl_3 part of the molecule will contribute about 2 D to the moment, it is evident that the M–Pt bond, so far as gross electron transfer is concerned, is essentially a single co-ordinate bond.[5]



(3) The redox potentials, which indicate that the electron density on the platinum atom is lower in the amine and sulphide complexes than in the phosphine and arsine complexes, which we consider to contain the stronger π-type bonds.

It is now fairly certain that in the platinous complexes of the alkyls of the atoms, N, P, As, Sb, S, Se, and Te, the electron transfer in the co-ordinate bond, and its variation in a series of analogous compounds containing one or other of the above donor atoms, is largely inductive.

It seems reasonable to take the capacity of metal salts to form thermally stable carbonyl and olefin complexes, as a measure of the tendency of the acceptor atoms to form dative π-bonds. Metals in their *normal valency states* being considered, this criterion indicates that platinum(II) has one of the strongest tendencies to co-ordinate by double bonds; yet even in platinum(II) complexes the electron transfer due to the π-type bond is rather small compared with the range of inductive effects of the various donor atoms. This is true even of the complexes of the trialkyl-phosphines and -arsines. Nevertheless, the π-type bond appears to be able to make a significant contribution to the metal–ligand bond strength in favourable circumstances. As evidence of this we have the difference in total bond strengths between *cis*- and *trans*-[$(MR_3)_2PtCl_2$] (M = P, As, or Sb; R = alkyl), which is [5] of the order of 10 kcal.

This paradox may be explained if we suppose that the release of electrons from metal to ligand in the dative π-bond, by decreasing the electronegativity of the ligand, induces an *almost equal* release of electrons from ligand to metal in the σ-bond. In this way the metal–ligand bond will be strengthened, but its electrical asymmetry will remain high. This seems to be the situation in most complex compounds of metals in their usual valency states when double co-ordinate bonding occurs.

Only exceptionally does the π-type co-ordinate bond appear to affect significantly the total transfer of charge between ligand and metal. The exceptional cases occur when the metal which must have filled *d*-orbitals is in an unusually low oxidation state, and/or when the donor atom which must have suitable vacant orbitals for dative π-bond formation is attached to very electronegative atoms or groups. This is evident from the low moments of such bonds as CO–Pt and PF_3–Pt.[12] Even in ethylene complexes, where dative π-bonding appears to be essential for stability but the carbon atoms are not attached to electronegative groups, the C_2H_4–Pt bond is still fairly dipolar, perhaps about 4 D. Here back-donation in the π-type bond is far from neutralising the forward-donation in the σ-bond.

[9] Jensen, *Z. anorg. Chem.*, 1936, **229**, 250.
[10] Chatt and Wilkins, *J.*, 1952, 273.
[11] Phillips, Hunter, and Sutton, *J.*, 1945, 146.
[12] Chatt and Williams, *J.*, 1951, 3061.

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The stabilisation of the exceptionally low oxidation states of metals with filled *d*-orbitals by such ligands as CO, PhNC, and PF_3 is undoubtedly due to the very poor availability of their lone pairs of electrons, together with their capacity to form strong dative π-bonds. Thus it is the result of a combination of very strong inductive withholding and mesomeric withdrawal of electrons from the metal atom by the ligands. However, when dative π-bonding is weak (*e.g.*, because the metal has not got all its *d*-orbitals filled, or the ligand has no suitable vacant orbitals), stabilisation of low-valency states against oxidation must generally be greatest in the case of complexes containing the most electronegative ligands which it is possible to attach to the metal in the low-valent state concerned. These ligands must often be amines, and undoubtedly $[V(dipyridyl)_3]^o$,[13] and the unstable $[Pt(NH_3)_4]^o$,[14] and $[Ir(NH_3)_5]^o$ [15] are somewhat stabilised by the inductive withholding of electrons from the metal atom. This will also be assisted by mesomeric withdrawal in the manner suggested by Burstall and Nyholm [16] in the case of $[V(dipyridyl)_3]^o$.

Experimental

Microanalyses are by Messrs. W. Brown and A. G. Olney of these laboratories.

The tri-*n*-propylphosphine complexes were prepared as described by Chatt and Wilkins,[17] and the di-*n*-propyl sulphide complexes as described by Rudelius.[18] The 4-*n*-pentylpyridine complexes were prepared as follows.

4-n-*Pentylpyridinium Chloroplatinite*, $[pepy\ H]_2[PtCl_4]$.—This *salt* was obtained as a pink precipitate by warming a solution of potassium chloroplatinite (5 g.) and 4-*n*-pentylpyridinium chloride (5 g.) in water (50 c.c.) for a few minutes. It was removed, washed with water, ethanol, and ether, and dried (7·3 g.), m. p. 175—178° (decomp.), sinters at 172—175° (Found: C, 37·8; H, 4·9. $C_{20}H_{32}N_2Cl_4Pt$ requires C, 37·7; H, 5·1%).

trans-*Di*-(4-n-*pentylpyridine*)*dichloroplatinum*, *trans*-$[pepy_2PtCl_2]$.—A suspension of the above chloroplatinite (7·0 g.) in di-*n*-butyl ether (100 c.c.) was boiled under reflux for 3 hr. The hot yellow solution was treated with a little charcoal, filtered, and allowed to cool. The *product* (3·5 g.) separated in thick yellow needles. Repeatedly recrystallised from carbon tetrachloride it had m. p. 140—141° (Found: C, 42·5; H, 5·2. $C_{20}H_{30}N_2Cl_2Pt$ requires C, 42·5; H, 5·35%). It is a non-electrolyte in nitrobenzene and its obvious physical properties together with a rough measurement of its dipole moment confirm its *trans*-configuration.

trans-*Di*-(4-n-*pentylpyridine*)*tetrachloroplatinum*, *trans*-$[pepy_2PtCl_4]$.—The preceding *trans*-salt (3·9 g.) in carbon tetrachloride (250 c.c.) was treated at 0° with chlorine (0·36 g.) in carbon tetrachloride (10 c.c.). A yellow solid separated. After 1 hr. the solid (2·5 g.) was removed. Repeatedly recrystallised from acetone (charcoal), then from ethyl acetate it had m. p. 250—251° (Found: C, 37·8; H, 4·7. $C_{20}H_{30}N_2Cl_4Pt$ requires C, 37·8; H, 4·8%). It is a non-electrolyte in nitrobenzene. It is better obtained by reactions exactly analogous to those used to prepare the platinous derivative. 4-n-*Pentylpyridinium chloroplatinate*, $[pepy\ H]_2[PtCl_6]$ (4·5 g.), was obtained as an orange precipitate on mixing aqueous solutions (25 c.c. each) of sodium chloroplatinate (3 g.) and 4-*n*-pentylpyridinium chloride (2·5 g.). It sinters at 200—210° and melts with gas evolution 213—220° (Found: C, 34·1; H, 4·5. $C_{20}H_{33}N_2Cl_6Pt$ requires C, 33·9; H, 4·55%). It (5·7 g.) was decomposed by boiling its xylene (250 c.c.) suspension under reflux for 22 hr. The brown solution was treated with charcoal, filtered, and taken to dryness at 15 mm. The residue, repeatedly recrystallised from ethyl acetate, gave pure *trans*-$[pepy_2PtCl_4]$ (2 g.), m. p. 251—252·5°.

Pyridine and ammonia complexes were prepared, but they were too insoluble in the aqueous phenol solvent to make any measurements with them.

Measurements of the Redox Potentials.—Solutions. The solvent (phenol 75%, water 25%) was prepared from dried "AnalaR" phenol (colourless, m. p. 40·9°) and distilled water. Two preparations of tetraethylammonium chloride were used; analysed by an ion-exchange method they had equiv. 235·5 and 235·9 (Calc. for $C_8H_{20}NCl,4H_2O$: equiv., 237·8). This salt was made

[13] Herzog, *Naturwiss.*, 1956, **43**, 35.
[14] Watt, Walling, and Mayfield, *J. Amer. Chem. Soc.*, 1953, **75**, 6175.
[15] Watt and Mayfield, *ibid.*, p. 6178.
[16] Burstall and Nyholm, *J.*, 1952, 3570.
[17] Chatt and Wilkins, *J.*, 1951, 2532.
[18] Rudelius, *Acta Univ. Lund*, 1885—6, **22**, Part 2, Paper 4.

up to 0·1M in the above solvent. Standard solutions of the platinous complexes were prepared in the above salt solution, 0·008M in the case of the less soluble Pt(IV) complexes and 0·024M in the case of the Pt(II) complexes. These solutions were mixed in the desired proportions to provide the electrolyte for the redox cell.

Redox cell. The redox electrodes were of platinum foil plated at a current density of 1 mA/cm.^{2} for 1—2 hr. in a gilding solution, prepared as described by Popoff, Kunz, and Snow.[19] The reference electrodes, Ag,AgCl, were prepared according to Brown's method.[20] The cell consisted of a small glass vessel containing two sets of electrodes, a nitrogen inlet tube, and an outlet tube. It was maintained at 25°. The solutions were mixed initially by bubbling pre-saturated nitrogen through them, then during the remainder of the experiment nitrogen was passed over them.

Measurements. The potentials of the two sets of electrodes were measured by a Tinsley Type 3126 B Vernier Potentiometer. The gold electrode was the positive electrode. The cell was sensitive to daylight; its e.m.f. increased with the strength of illumination, but its response to increased illumination was rather sluggish. The redox electrode must have been the source of light sensitivity, because when the Ag,AgCl electrodes were replaced by a salt bridge to an external calomel electrode the cell remained sensitive to light. All the following experiments were carried out in the dark or in dull artificial light, with the cell wrapped in tin foil.

The e.m.f. of the cell was very slow in reaching its equilibrium value (1—5 days). This was certainly due to the slow equilibration of the redox electrodes and the solution, because equilibrium was established equally slowly after the Ag,AgCl electrode had been replaced by an external calomel electrode. Bright platinum foil in place of the gold electrode was equally slow in coming to equilibrium. Platinised platinum electrodes appeared to catalyse some

TABLE 2. *Variation with time of the e.m.f. of the cell containing trans-*$[(Pr^n_2S)_2PtCl_4]$ (0·0074M) and *trans-*$[(Pr^n_2S)_2PtCl_2]$ (0·0062M).

Time (hr.)	0	0·42	0·58	5·0	16	29·5	47	65·5	87·5	96	112	136	144	160
E.m.f. (mv)	—	335·0	344·4	395·2	413·8	421·3	426·5	430·5	433·9	434·9	437·3	439·3	439·5	438·8

TABLE 3. *Equilibrium potentials* (E) *and redox potentials* (E_0).

(C_{IV} = molarity of Pt(IV) complex, C_{II} = molarity of Pt(II) complex.)

System: *cis-*$[(PPr^n_3)_2PtCl_4]$–*cis-*$[(PPr^n_3)_2PtCl_2]$.

Expt.	Electrode pair	10^3C_{IV}	10^3C_{II}	E	E_0
IA	1	7·4	6·15	370	368
	2	7·4	6·15	371	369
IB	1	4·95	12·3	351	363
	2	4·95	12·3	354	366
II	1	6·0	6·0	362	362
	2	6·0	6·0	363	363
III	1	6·0	6·0	372	372
	2	6·0	6·0	373	373
				Mean E_0	367

System: *trans-*$[(Pr^n_2S)_2PtCl_4]$–*trans-*$[(Pr^n_2S)_2PtCl_2]$.

Expt.	Electrode pair	10^3C_{IV}	10^3C_{II}	E	E_0
IA	1	6·0	6·0	439	439
	2	6·0	6·0	442	442
IB	1	4·8	9·6	434	443
	2	4·8	9·6	432	441
II *	1	6·0	6·0	440	440
				Mean E_0	441

* Electrode 2 of experiment II did not work.

System: *trans-*$[(PPr^n_3)_2PtCl_4]$–*trans-*$[(PPr^n_3)_2PtCl_2]$.

Expt.	Electrode pair	10^3C_{IV}	10^3C_{II}	E	E_0
IA	1	6·0	6·0	350	350
	2	6·0	6·0	350	350
IB	1	4·8	9·6	340	349
	2	4·8	9·6	339	348
				Mean E_0	349

System: *trans-*$[pepy_2PtCl_4]$–*trans-*$[pepy_2PtCl_2]$.

Expt.	Electrode pair	10^3C_{IV}	10^3C_{II}	E	E_0
IA	1	6·0	6·0	477	477
	2	6·0	6·0	471	471
IB	1	4·8	9·6	472	481
	2	4·8	9·6	463	472
				Mean E_0	475

reaction in the solution leading to a very rapid decrease in the e.m.f. The addition of a trace (<1 mM) of ferrous salt in an attempt to promote equilibration between gold electrode and solution was also unsuccessful.

After the cell had been made up, both pairs of electrodes registered potential differences

[19] Popoff, Kunz, and Snow, *J. Phys. Chem.*, 1928, **32**, 1056.
[20] Brown, *J. Amer. Chem. Soc.*, 1934, **56**, 646.

50—100 mv lower than those finally obtained. The e.m.f.s increased for a few days, the two pairs of electrodes recording different e.m.f.s and showing different rates of potential drift, but both finally approached the same value within a few mv of their final value after 1—5 days. New electrodes reached equilibrium more rapidly than used ones, but reached the same equilibrium potential in the same solution. Old electrodes finally became poisoned and then the potentials drifted comparatively rapidly and erratically; they were then discarded. Sometimes the potential of the cell overshot the equilibrium potential by a few mv, so that equilibrium was finally approached from the higher potential side; such behaviour is indicative of the presence of a minute amount of a minor redox system.[21] In spite of the sluggish behaviour of the cell the final potentials obeyed Nernst's law and gave different E_0 values for the different pairs of complexes, indicating that the equilibrium potentials were indeed redox potentials governed by the main redox components. A typical example showing the slow approach to constant e.m.f. is given in Table 2 and the results of our measurements in Table **3.**

In Table 3, experiments IB were conducted with the same cell as IA, but with the addition of a further quantity of the solution of the Pt(IV) complex after equilibrium had been reached in experiment IA. A change of Roman numeral in the first columns denotes that fresh solutions were used.

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[*Received, August 24th,* 1956.]

[21] Ahrland and Larsson, *Acta Chem. Scand.*, 1954, **8**, 137.

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262. *Absorption Spectra of Some Sulphoxides in the Near Ultraviolet Region.*

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Apart from any modification that conjugation may impose, the sulphoxide group itself is a chromophore producing moderately strong absorption near 220 mμ. It is suggested that the transition is one of an electron of the unshared $3sp^3$ pair of the sulphur atom into an appropriately oriented $3d$ sulphur orbital, *i.e.*, a transition between molecular orbitals of which these atomic orbitals are the main components. In a phenyl sulphoxide this transition would couple strongly with a B_{2u}-like transition of the benzene ring because the local transition moments would be parallel; and in a *para*-substituted phenyl sulphoxide it would couple strongly with the B_{2u}-derived transition of the corresponding monosubstituted benzene for the same reason. In *ortho*- and *meta*-substituted phenyl sulphoxides this coupling is expected to be considerably weaker, because the local transition moments are no longer parallel, and for steric reasons. The absorption spectra of a large number of aryl, diaryl, aralkyl, diaralkyl, and aralkyl aryl sulphoxides are recorded, and can be reasonably interpreted on the basis of the electronic assignment mentioned.

WE have extended our study of ultraviolet spectra of organic sulphur compounds (sulphides,[1] sulphones,[2] and thiosulphones [3]) to sulphoxides. Sulphoxides R_2SO, unlike the other classes of sulphur compounds mentioned, even when both radicals R are fully saturated, possess a moderately strong absorption band in the quartz ultraviolet region.[4]

[1] Mangini and Passerini, *J.*, 1952, 1168; *J. Phys. Radium*, 1954, **15**, 625; *Experientia*, 1956, **12**, 49; *J.*, 1956, 4954; Mangini *et al.*, *Gazzetta*, 1954, **84**, 3, 36, 47, 606.
[2] *Idem, ibid.*, p. 73.
[3] Leandri, Mangini, and Tundo, *J.*, 1957, 52.
[4] Koch, *J.*, 1950, 2892.

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In non-polar solvents such as *cyclo*hexane the absorption maximum is near 220 mμ (log ε, *ca.* 3·30); in hydroxylic solvents this band is often at appreciably shorter wavelengths.[4, 5]

We have studied the spectra of methyl phenyl, benzyl phenyl, dibenzyl, and diphenyl sulphoxides and many of their substitution products. To simplify discussion we consider first the nature of the fundamental sulphoxide transition. We cannot deduce this from the spectra, but we can make a plausible suggestion, and then show that this enables many features of the spectra to be understood.

Bond lengths, bond angles, and dipole moments of sulphoxides, and the fact that sulphoxides can be optically resolved, indicate, as a first approximation, that the ground state of the valency shell of the sulphur aton can be described as an octet with $3sp^3$ hybridisation in the bonds and also in the unshared electron pair. To improve this description two further interactions may be taken into account. The first, conjugation of the unshared $3sp^3$ electron pair of sulphur with 2π electron shell of the unsaturated group, applies only when at least one of the groups R is unsaturated at the point of its attachment to sulphur, but it may then be quite important. The other effect, conjugation between one pair of unshared $2p$ electrons of oxygen with a vacant $3d$ orbital of sulphur, is universal, but is weak in sulphoxides (considerably weaker than in sulphones) or in sulphur groups containing still more oxygen, the extreme case being the sulphate ion. This could be restated by saying that two pairs of electrons which we started by calling unshared are really weakly π-bonding, one pair between S and C, and the other between O and S.

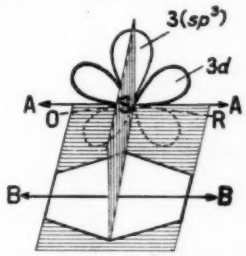

FIG. 1.
A—A Direction of transition moment $3(sp^3) \longrightarrow 3d$ of sulphur.
B—B Direction of transition moment $A_{1g} \longrightarrow B_{2u}$ of benzene.

To approach the description of the transition, and of the upper state, from our first approximation to the ground state, we suggest that, since the highest occupied orbital of the latter will be the non-bonding $3sp^3$ sulphur orbital and the lowest unoccupied orbital will be one of the $3d$ sulphur orbitals, the transition in this approximation is $(3sp^3)^2 \rightarrow (3sp^3)(3d)$. As the transition is strong we assume that it is an allowed singlet–singlet transition; the upper orbital should be antisymmetric to a plane of symmetry of the lower, which, from what we have said, is the plane shown as vertical in Fig. 1. Thus the transition moment is perpendicular to this plane, and therefore, in a phenyl sulphoxide, parallel to the transition moment of the B_{2u}-like first singlet–singlet transition of the benzene ring. This is an expected symmetry relation to which reference will be made in discussing the spectra. Of course, the upper state ought to be described more accurately. The orbital which the optical electron enters is, from a spectroscopic viewpoint, a weakly antibonding molecular orbital, centred mainly on sulphur; but that makes no difference to the symmetry relation mentioned.

Data for the measurable critical points of the spectra are shown in Tables 1—4. In these nearly structureless band-systems small inflexions or changes of slope that can be seen but not measured have to be examined. Some curves are shown in Figs. 2—5. For comparison, data for some corresponding sulphones have also been included to show the different solvent effect occurring between the two series of compounds.

Unsubstituted Aromatic Sulphoxides.—The simplest situation arises in dibenzyl sulphoxide; as the benzene rings and the sulphoxide group are isolated, its spectrum

[5] McConnell, *J. Chem. Phys.*, 1952, **20**, 700.

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(Table 1, Fig. 2) is essentially that of an aliphatic sulphoxide with the superposed, relatively weak, B_{2u}-like benzene transition appearing at its long-wave length end. There is no indication of interaction between the sulphoxide and benzenoid excitations.

In methyl phenyl and benzyl phenyl sulphoxide conjugation between a benzene ring

TABLE 1. *Alkyl aryl sulphoxides and sulphones.*

No.		M. p. or b. p.	*cyclo*Hexane λ (mμ)	*cyclo*Hexane log ε	Ethanol λ (mμ)	Ethanol log ε
(1)	Dibenzyl sulphoxide	m. p. 133°	(<210)	—	(215	4·25)
			222	4·26	222	4·29
					(257	2·58)
			265	2·90 [c]	260	2·68
					265	2·55 [b]
(2)	Methyl phenyl sulphoxide [a]	b. p. 144°/15 mm.	(232	3·29)	(226	3·51)
			253	3·60	238	3·61
					256	3·45 [b]
(3)	Benzyl phenyl sulphoxide	m. p. 124°	(246	3·54)	(237	3·66)
			261	3·71	248	3·76
			280	3·50 [b]		
(4)	Diphenyl methylene disulphoxide ...	m. p. 194°	—	—	(235	3·83)
					249	3·94
(5)	Benzyl phenyl sulphone †	m. p. 148°	(<212)	—	(<215)	—
			217	4·18	219	4·12
			(250	2·73)	(250	2·45)
			255	2·80 [c]	255	2·60 [c]
			259	2·93	259	2·85
			(262	2·88)	(263	2·80)
			265	3·06	265	3·03
			(269	2·74)	(270	2·73)
			272	2·94	272	2·90
(6)	Diphenyl methylene disulphone ‡ ...	m. p. 119—120°	—	—	222	4·29
					(240	2·13)
					260	3·19 [c]
					(262	3·16)
					267	3·36
					(270	3·16)
					274	3·29

[a] Inflexion. [b] Shoulder. [c] Small pronounced max. preceded by inflexions at 250 and 256 mμ.

[a] For spectrum in ethanol, see also Koch, *J.*, 1950, 2892; in ethanol and NaOEt the spectra are practically identical.

† Spectrum in ethanol, see also Fehnel and Carmack, *J. Amer. Chem. Soc.*, 1949, **71**, 236.

‡ In ethanol and NaOEt, single band, $\lambda_{max.}$ 267 (log ε = 3·80); $\lambda_{min.}$ 241 mμ (log ε = 3·56). For spectrum in ethanol see also Fehnel and Carmack, *loc. cit.*

Preparations. (1) Hinsberg, *Ber.*, 1908, **41**, 2838. (2) See Experimental. (3) Pummerer, *Ber.*, 1910, **43**, 1401. (4) Hinsberg, *J. prakt. Chem.*, 1912, **85**, 337. (5) R. Otto and W. Otto, *Ber.*, 1888, **21**, 1695. (6) *Idem, ibid.*, p. 346.

and the sulphoxide group is structurally possible. The spectra (Table 1, Fig. 2) show evidence of strong interaction between the local excitations, in the form of a great transfer of intensity from the stronger (in our interpretation allowed) sulphoxide region to the weaker (in benzene forbidden) benzene region. This transfer amounts to a merging of the two bands to give one with its maximum well towards the benzene region. The strong coupling implies marked non-orthogonality between the parent sulphoxide and benzene transitions; in fact, we made this a maximum by making the moments parallel in our preliminary description of their nature in the absence of interaction.

In the more complicated case of diphenyl sulphoxide, where the situation just described is duplicated, the resonance of the sulphoxide group with one benzene ring is exactly degenerate with its resonance with the other. This should give the single resonance band already described with a doubled intensity (log ε larger by 0·3), but, as the sulphoxide group is common, the two resonance systems will interact and a new resonance will split the degenerate band into two. The observed spectra (Table 2, Fig. 3) show the splitting.

TABLE 2. *Diaryl sulphoxides.*

No.	M. p. or b. p.	*cyclo*Hexane λ (mμ)	*cyclo*Hexane log ε	Ethanol λ (mμ)	Ethanol log ε
(7) Diphenyl †	m. p. 71°	(219	4·10)	(220	4·05)
		226	4·13	233	4·15
		267	3·42 [a]	265	3·32 [b]
(8) Phenyl *o*-tolyl	m. p. 42°	228	4·07 [c]	(223	4·04)
		280	3·17 [b]	235	4·16
				265	3·38 [d]
(9) Phenyl *m*-tolyl	m. p. 46—47°	230	4·11 [b]	(225	4·10)
		278	3·30 [b]	233	4·14
				270	3·29 [b]
(10) Phenyl *p*-tolyl	m. p. 72°	(223	3·97)	(222	4·01)
		233	4·05	237	4·20
		270	3·28 [a]	270	3·28 [a]
(11) Di-*o*-tolyl	m. p. 121°	227	4·05 [a]	(224	4·00)
		245	3·85 [a]	237	4·16
		270	3·38 [a]	(260	3·29)
		(277	3·27)	274	3·43
		280	3·28 [a]	282	3·30 [b]
(12) Di-*m*-tolyl	b. p. 215°/15 mm.	230	4·07 [b]	(228	4·28)
		(269	3·41)	235	4·21
		270	3·42 [a]	(268	3·59)
		(277	3·27)	270	3·61 [c]
		278	3·28 [a]	(278	3·48)
				280	3·49 [a]
(13) Di-*p*-tolyl	m. p. 96°	(221	4·11)	(224	4·10)
		237	4·20	240	4·27
		275	3·35 [b]	275	3·35 [b]
(14) *o*-Chlorophenyl phenyl	m. p. 61°	(226	4·12)	(225	4·10
		230	4·13 [c]	235	4·17
		265	3·45 [a]	265	3·35 [b]
(15) *m*-Chlorophenyl phenyl	m. p. 39—40°	—	*e*	232	4·11 [b]
		273	3·35 [f]	268	3·30 [b]
		281	3·12 [f]		
(16) *p*-Chlorophenyl phenyl	m. p. 45—46°	(220	4·05)	(222	4·06)
		234	4·20	239	4·26
		280	3·16 [b]	275	3·20 [b]
(17) Di-*p*-chlorophenyl	m. p. 142°	221	4·18 [c]	(225	4·08)
		240	4·29	244	4·34
		280	3·40 [b]	260	3·78 [g]
(18) Di-*p*-bromophenyl	m. p. 151—152°	(219	4·15)	227	4·20 [a]
		226	4·19 [a]	248	4·42
		(231	4·18)	268	3·75 [a]
		248	4·34		
		268	3·75 [g]		
(19) *p*-Aminophenyl phenyl *	m. p. 150°	(229	3·81)	(238	3·78)
		259	4·21	278	4·21
		290	3·57 [b]		
(20) Di-*p*-aminophenyl *	m. p. 175°	—	—	(238	3·80)
				264	4·17
				(275	4·13)
				300	4·25
(21) *p*-Aminophenyl benzyl *	m. p. 197—198°	(232	4·08)	(237	3·68)
		242	4·12	273	4·26
		(250	4·00)	300	3·80 [a]
		265	4·25		
		300	3·50 [d]		

[a] Inflexion. [b] Shoulder. [c] Slightly pronounced max. [d] Nearly flat shoulder at 269—279 mμ. [e] 230 mμ band absent. [f] Nearly flat region. [g] Weak shoulder.

* Arbitrary extinction values in *cyclo*hexane solution.

† In H_2SO_4 (50% by vol.): $\lambda_{infl.}$ 228 (log ε 4·08); $\lambda_{max.}$ 274 (log ε 3·49); for spectrum in ethanol, see Gibson *et al.*, *J.*, 1923, **123**, 874; Chaix, *Bull. Soc. chim. France*, 1933, **53**, 700; Koch, *J.*, 1950, 2892.

Preparations. (7) Colby and McLoughlin, *Ber.*, 1887, **20**, 198. (8—9) Courtot and Frenkiel, *Comp. rend.*, 1934, **199**, 557. (10) Chaix, *Bull. Soc. chim. France*, 1933, **53**, 700. (11—12, 14—17, 21) See Experimental. (13) Parker, *Ber.*, 1890, **23**, 1845. (18) Boeseken and Watermann, *Rec. Trav. chim.*, 1911, **30**, 130. (19) Hinsberg, *Ber.*, 1903, **36**, 113. (20) Gazdar and Smiles, *J.*, 1908, **93**, 1835.

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TABLE 3. *Aryl benzyl sulphoxides.*

		*cyclo*Hexane		Ethanol	
No.	M. p.	λ (mμ)	log ε	λ (mμ)	log ε
(22) Methyl *p*-nitrophenyl	151—152°	(223	3·78)	(225	3·75)
		244	3·94	248	3·88
		(271	3·42)	(270	3·73)
		296	3·75	284	3·78
(23) Benzyl *p*-nitrophenyl	168—169	(225	4·10)	226	4·13 [b]
		232	4·13 [a]	246	3·94 [b]
		251	3·96 [c]	—	—
		(277	3·53)	(270	3·75)
		305	3·74	293	3·85
(24) *p*-Nitrobenzyl phenyl	161—162	(237	3·86)	(233	3·81)
		259	3·99	278	4·02
		(280	3·92)	330	3·15 [c]
		290	3·96		
(25) *p*-Nitrobenzyl *p*-nitrophenyl *	181—182	(228	4·03)	(232	3·98)
		251	4·18	254—270	4·14 [c]
		(272	4·05)	285	4·18
		280	4·08 [d]		
(26) *p*-Nitrobenzyl *p*-nitrophenyl ‡	161—162	(245	3·90)	(240	3·67)
		266	4·05	272	4·05
		290	3·90 [a]		
(27) Di-*p*-nitrobenzyl	216—217	absolutely insoluble		(232	3·30)
				277	4·03
(28) *o*-Nitrophenyl phenyl	—	(238	4·03)	225	4·23 [c]
		244	4·05 [a]	270	3·80 [c]
		300	3·40 [f]	315	3·34 [c]
(29) Di-*o*-nitrophenyl	188—189	(234	4·09)	230	4·20 [a]
		248	4·14		
		295	3·45 [h]		
(30) *m*-Nitrophenyl phenyl	76—77	<(215)	—	229	4·30 [a]
		225	4·29 [a]	250	4·03 [c]
		245	4·12 [b]	262	3·96 [c]
		258	4·00 [c]	295	3·15 [b]
		295	3·02 [b]		
(31) *p*-Nitrophenyl phenyl †	107—108	(235	3·83)	(238	3·87)
		260	4·08	265	4·06
		295	3·65 [c]	290	3·86 [c]
				330	2·95 [b]
(32) Di-*p*-nitrophenyl ‡	179—180	(224	4·07)	(230	4·00)
		257	4·28 [i]	271	4·27
		273	4·20 [i]	345	2·90 [b]

[a] Slightly pronounced max. [b] Inflexion. [c] Shoulder. [d] Broad max., flat region 275—295 mμ (log ε = 4·05). [e] Flat region with broad max. at 256 mμ. [f] Very weak inflexion. [g] Flat region and irregular feature with hint of max. at 330 mμ. [h] Shoulder, with irregular feature towards the red. [i] Broad max. Nearly flat region at 273—281 mμ.

* In aqueous 0·1N-NaOH: only one max. at 285 mμ (log ε = 4·19).
† In conc. H_2SO_4: $\lambda_{max.}$ 270° (log ε 4·36).
‡ Saturated *cyclo*hexane solution, arbitrary extinction values.

Preparations. (22—28, 30) See Experimental. (29) Leandri and Pallotti, *Boll. sci. Fac. chim. ind. Bologna*, 1955, **13**, 48. (31—32) Szmant and McIntosh, *J. Amer. Chem. Soc.*, 1951, **73**, 4356.

[The general banking of intensity towards shorter wavelengths is probably due to interaction between the two equivalent systems.] The spectrum therefore ought to be approximately the same as for methyl phenyl sulphoxide (Table 1, Fig. 2), except that the intensity should be doubled, *i.e.*, log ε should be 0·3 unit greater than for the simpler molecule. This is, in fact, a fairly accurate description of the observed spectrum.

The coupling of the unshared electrons of sulphur with the benzene ring is also supported by some chemical evidence such as the *para*-orienting effect of the sulphoxide group in nitration in the phenyl series (in nitric acid solution).[5a]

[5a] Leandri and Pallotti, *Boll. sci. Fac. chim. ind. Bologna*, 1955, **13**, 48.

Methyl- and Halogen-substituted Aromatic Sulphoxides.—Spectra are recorded in Table 2 and Fig. 3. The main points about them are as follows:

Methyl and halogen substituents in *para*-positions, even when there are two of them, make only very minor differences to the spectra, which are essentially those of the parent compounds. One and, still more, two *ortho*-substituents cause the long-wavelength benzene band-system to be less intense in the phenyl sulphoxide resonance system. This could be understood on the basis of *ortho*-substituents' twisting the aryl groups sufficiently partly to uncouple the local excitations of the phenyl and sulphoxide groups. However, the fact that one, and still more two, *meta*-substituents act in the same way, and almost as efficiently as *ortho*-substituents, is more difficult to explain on stereochemical grounds,

TABLE 4. *Aryl benzyl sulphones.*

		*cyclo*Hexane		Ethanol	
No.	M. p.	λ (mμ)	log ε	λ (mμ)	log ε
(33) Methyl *p*-nitrophenyl	104°	(218	3·57)	255	3·83
		248	4·05		
		279	3·25 [c]		
		(285	3·18)		
		287	3·20		
		298	2·90 [b]		
(34) Benzyl *p*-nitrophenyl *	172—173	(229	4·10)	(228	3·97)
		247	4·25	250	4·25
		280	3·65 [c]	286	3·67 [c]
(35) *p*-Nitrobenzyl phenyl *	209	(232	3·58)	(234	3·47)
		264	4·09	269	4·09 [c]
		285	3·78 [b]	(270	4·07)
				272	4·09 [c]
(36) *p*-Nitrobenzyl *p*-nitrophenyl *	195	(224	3·90)	(225	3·83)
		253	4·28	260	4·27
		278	3·86 [b]		

[a] Broad inflexion preceded by shoulder at 330 mμ (log ε = 4·10), and followed by inflex. at 360 mμ (log ε, 3·20) etc. [b] Very weak inflexion. [c] Inflexion. [d] Nearly flat region followed by weak max. at 287 mμ. [e] Small pronounced maximum.

* Saturated *cyclo*hexane solution, arbitrary extinction values.

Preparations. (33) Gaber and Crünberg, *J. Appl. Chem. U.S.S.R.*, 1939, **12**, 1481. (34) Zincke and Lehnardt, *Annalen*, 1913, **400**, 16; For spectrum in ethanol see Fehnel and Carmack, *J. Amer. Chem. Soc.*, 1949, **71**, 84. (35—36) See Experimental.

unless we can assume that the repulsion of the sulphoxide oxygen atom, as an anionic (electron-swollen) atom, extends considerably beyond the usually accepted van der Waals radius.

However, the above facts are open to an electronic interpretation based on the consideration that the B_{2u}-derived local benzenoid excitation would, in an *ortho*- or *meta*-substituted phenyl sulphoxide, no longer have a transition moment parallel to that of the local sulphoxide transition: for the former will deviate towards perpendicularity with the line of bonding of the *ortho*- or *meta*-substituent. Coupling between the local transition moments must therefore be considerably weakened. If we adopt this interpretation, we must assume that the uncoupling, resulting from the diminished non-orthogonality, is quantitatively sufficient to allow the weaker local transition to reproduce itself more or less recognisably and separately in the spectra.

Nitro-substituted Aromatic Sulphoxides.—In compounds containing a *p*-nitrobenzyl group (Table 3, Fig. 4) the nitro-group has no continuous connexion through a π-electron shell with the sulphoxide group. Accordingly, the spectra are much as one would suppose from the preceding discussion, given that the long-wavelength local chromophore is that of nitrobenzene, rather than that of benzene, and is thus the source of a longer-wavelength (near 290 mμ) and more intense absorption than that due to the unsubstituted benzene ring.

In *p*-nitrophenyl phenyl sulphoxides where there is the possibility of through-conjugation between the nitro- and the sulphoxide group (Table 3, Figs. 4, 5), the spectra

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suggest that such through-conjugation functions, though only moderately strongly: we see sometimes one very broad band, sometimes two merged and unresolved bands, extending, with a continuously maintained high intensity, over the phenyl sulphoxide and nitrobenzene regions of the spectrum.

ortho-Nitrophenyl phenyl sulphoxides (Table 3, Fig. 5) show a remarkable reduction in the intensity of absorption in the longer wavelength spectral region of the nitrobenzene

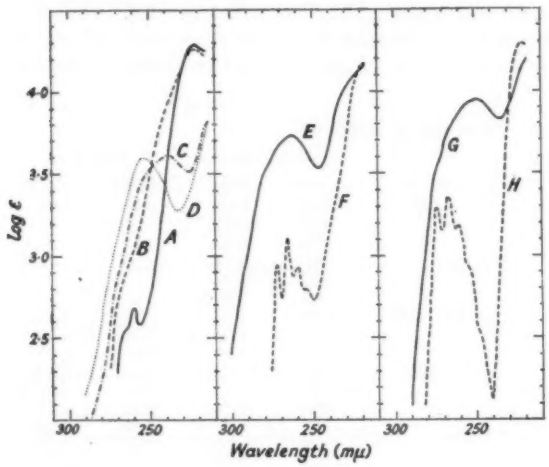
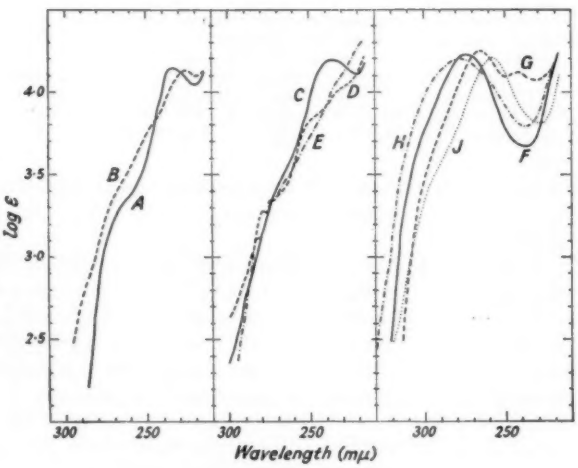


FIG. 2.
A, $(Ph{\cdot}CH_2{\cdot})_2SO$ in ethanol.
B, $(Ph{\cdot}CH_2{\cdot})_2SO$ in *cyclo*hexane.
C, Ph·SO·Me in ethanol.
D, Ph·SO·Me in *cyclo*hexane.
E, $Ph{\cdot}SO{\cdot}CH_2Ph$ in *cyclo*hexane.
F, $Ph{\cdot}SO_2{\cdot}CH_2Ph$ in *cyclo*hexane.
G, $Ph{\cdot}SO{\cdot}CH_2{\cdot}SO{\cdot}Ph$ in ethanol.
H, $Ph{\cdot}SO_2{\cdot}CH_2{\cdot}SO_2{\cdot}Ph$ in ethanol.

FIG. 3.
A, Ph_2SO in ethanol.
B, Ph_2SO in *cyclo*hexane.
C, $(p\text{-}Me{\cdot}C_6H_4{\cdot})_2SO$ in *cyclo*hexane.
D, $(o\text{-}Me{\cdot}C_6H_4{\cdot})_2SO$ in *cyclo*hexane.
E, $m\text{-}Cl{\cdot}C_6H_4{\cdot}SO{\cdot}Ph$ in *cyclo*hexane.
F, $Ph{\cdot}CH_2{\cdot}SO{\cdot}C_6H_4{\cdot}NH_2\text{-}p$ in ethanol.
G, $Ph{\cdot}CH_2{\cdot}SO{\cdot}C_6H_4{\cdot}NH_2\text{-}p$ in *cyclo*hexane.
H, $Ph{\cdot}SO{\cdot}C_6H_4{\cdot}NH_2\text{-}p$ in ethanol.
J, $Ph{\cdot}SO{\cdot}C_6H_4{\cdot}NH_2\text{-}p$ in *cyclo*hexane.

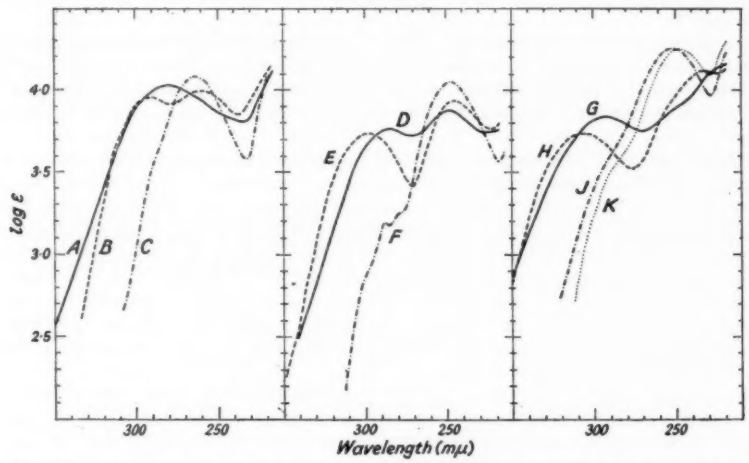


chromophore, obviously owing to steric twisting of the nitro-group, with partial breakdown of its conjugation with the aromatic π-shell.

Amino-substituted Aromatic Sulphoxides.—Of those studied (Table 2, Fig. 3), all contain the *p*-aminophenyl sulphoxide system. Inasmuch as the sulphoxide group has unfilled sulphur 3*d* orbitals, as well as some double bonding between sulphur and oxygen, some degree of through-conjugation between the electron-donating amino-group and the *para*-sulphoxide group is possible. Even though the electron displacement is opposite in

direction to that due to a conjugated *para*-nitro-group, one might expect the *para*-amino-group to exert somewhat similar spectral effects. In fact we see a large red-shift of the main band, which covers with high intensity the normal long-wavelength region of the aniline chromophore. In the spectrum of di-*p*-aminophenyl sulphoxide there are two

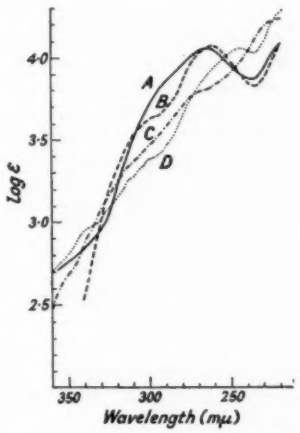
FIG. 4.



A, Ph·SO·CH_2·C_6H_4·NO_2-*p* in ethanol; *B*, Ph·SO·CH_2·C_6H_4·NO_2-*p* in *cyclo*hexane; *C*, Ph·SO_2·CH_2·C_6H_4·NO_2-*p* in *cyclo*hexane; *D*, Me·SO·C_6H_4·NO_2-*p* in ethanol; *E*, Me·SO·C_6H_4·NO_2-*p* in *cyclo*hexane; *F*, Me·SO_2·C_6H_4·NO_2-*p* in *cyclo*hexane; *G*, Ph·CH_2·SO·C_6H_4·NO_2-*p* in ethanol; *H*, Ph·CH_2·SO·C_6H_4·NO_2-*p* in *cyclo*hexane; *J*, Ph·CH_2·SO_2·C_6H_4·NO_2-*p* in ethanol; *K*, Ph·CH_2·SO_2·C_6H_4·NO_2-*p* in *cyclo*hexane.

FIG. 5.

A, Ph·SO·C_6H_4·NO_2-*p* in ethanol.
B, Ph·SO·C_6H_4·NO_2-*p* in *cyclo*hexane.
C, Ph·SO·C_6H_4·NO_2-*o* in ethanol.
D, Ph·SO·C_6H_4·NO_2-*p* in *cyclo*hexane.



resolved bands of similar intensity, owing to the equivalence and overlapping of the constituent *p*-aminophenyl sulphoxide chromophores, as arose with the parent substance.

EXPERIMENTAL

Absorption spectra were recorded with a Hilger Uvispek photoelectric spectrophotometer in B.D.H. *cyclo*hexane and 95% ethanol, specially purified for spectroscopy. Concentrations were 10^{-2} g./l. except for compounds only slightly soluble in *cyclo*hexane, for which saturated solutions were used and arbitrary log values calculated.

In the Tables minima are in parentheses; shoulders or inflexions have been indicated.

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Materials.—Methyl phenyl sulphoxide. Methyl phenyl sulphide (5 g.) was oxidised at 10—20° with peracetic acid [*i.e.*, hydrogen peroxide (4 c.c.; 32%) in glacial acetic acid (100 c.c.)] for a few hours. The solution was diluted to 500 c.c with water and extracted with ether. The ethereal solution was washed with aqueous sodium carbonate (10%) and with water, dried (Na_2SO_4), and the ether was removed, the residue being fractionated *in vacuo*. The colourless oil had b. p. 144°/15 mm. [Van Hove [6] (who used nitric acid) reports 263·5—264°/760 mm.]

Di-o-tolyl sulphoxide. Prepared as above by oxidation of the corresponding sulphides the white di-*ortho*-compound, crystallised from light petroleum, had m. p. 121° (the product obtained by action of thionyl chloride on *ortho*-tolylmagnesium halide [7] had the same m. p.) and the di-*meta*-compound was a colourless oil which was distilled under reduced pressure, b. p. 215°/15 mm. (as in lit.[7]).

o-*Chlorophenyl phenyl sulphoxide.* To *o*-chlorobenzenesulphinyl chloride (17 g.), prepared by heating *o*-chlorobenzenesulphinic acid with thionyl chloride on a water-bath for 15 min. (yellowish oil, b. p. 112—113°/3 mm.) in benzene (50 c.c.) were added small quantities of anhydrous aluminium chloride (30 g.). After being heated for 45 min. the mixture was dropped into iced-water, the excess of benzene steam-distilled off, and the oil suspension extracted with ether, the ether finally being evaporated off. The residue was distilled under reduced pressure and gave an oil, b. p. 199°/4 mm., which became a white *solid*. Crystallisation from light petroleum gave prisms, m. p. 61° (Found: S, 13·65. $C_{12}H_9OClS$ requires S, 13·6%).

m-*Chlorophenyl phenyl sulphoxide*, prepared as for the *o*-isomer, crystallised from light petroleum as prisms, m. p. 39—40° (Found: S, 13·7. $C_{12}H_9OClS$ requires S, 13·6%).

p-*Chlorophenyl phenyl sulphoxide.* *p*-Chlorobenzenesulphinic acid, when treated with thionyl chloride, gave *p*-chlorobenzenesulphinyl chloride as a yellowish oil, b. p. 134°/8 mm. On treatment with aluminium chloride in benzene this gave an oil, b. p. 228°/16 mm., which solidified. Recrystallisation from light petroleum gave prisms, m. p. 45—46° (Bergmann and Tschudnowsky [8] report b. p. 228°/21 mm.).

Di-p-chlorophenyl sulphoxide. Aluminium chloride (30 g.) was added, with constant cooling and in small quantities, to chlorobenzene (100 c.c.) and thionyl chloride (15 g.). After 2 hr. on a water-bath, followed by steam distillation, this gave a solid which gave prisms, m. p. 142° (from ligroin). (Cf. ref. 9. Prepared by oxidation of the sulphide with peracetic acid [10] or with nitric acid,[11] it had m. p. 139° and 143° respectively.)

p-*Aminophenyl benzyl sulphoxide.* *p*-Aminophenyl benzyl sulphide (3·5 g.) in acetone (50 c.c.) was oxidised with hydrogen peroxide (1·5 c.c.; 30%). After a week at room temperature, acetone was removed *in vacuo* leaving white prismatic *needles*. Recrystallised from ethanol, these had m. p. 197—198° (Found: N, 6·2. $C_{13}H_{13}ONS$ requires N, 6·05%).

Methyl p-*nitrophenyl sulphoxide.* Methyl 4-nitrophenyl sulphide (10 g.) was oxidised in glacial acetic acid (100 c.c.) with hydrogen peroxide (7 c.c.; 30%). The product, needles (from benzene), had m. p. 151—152° (Zincke and Lenhardt [12] give m. p. 149°; oxidation was with nitric acid).

Benzyl 4-*nitrophenyl sulphoxide.* Benzyl *p*-nitrophenyl sulphide (6 g.), glacial acetic acid (400 c.c.), and hydrogen peroxide (2·5 c.c.; 32%) were kept for a week at room temperature. After dilution with water (1 l.) a yellowish precipitate separated which gave *plates*, m. p. 168—169° (from ethanol) (Found: S, 5·55. $C_{13}H_{11}O_3NS$ requires S, 5·4%).

By oxidation of the parent sulphide with peracetic acid the following products have been obtained: p-*Nitrobenzyl phenyl sulphoxide*, plates, m. p. 161—162° (from ethanol) (Found: N, 5·5. $C_{13}H_{11}O_3NS$ requires N, 5·4%). p-*Nitrobenzyl* p-*nitrophenyl sulphoxide*, needles, m. p. 181—182° (from ethanol) (Found: N, 9·2. $C_{13}H_{10}O_5N_2S$ requires N, 9·15%). *Benzyl* p-*nitrobenzyl sulphoxide*, yellowish prisms, m. p. 161—162° (from ethanol) (Found: N, 5·5. $C_{14}H_{13}O_3NS$ requires N, 5·1%). *Di*-p-*nitrobenzyl sulphoxide*, needles, m. p. 216—217° (from ethanol) [previously prepared [13] by electrolytic oxidation of di-*p*-nitrobenzyl sulphide

[6] Van Hove, *Bull. Acad. roy. Belg., Cl. Sci.*, 1926, **12**, 929; *Chem. Zentr.*, 1927, **98**, 1821.
[7] Courtot and Frenkiel, *Compt. rend.*, 1934, **199**, 557.
[8] Bergmann and Tschudnowsky, *Ber.*, 1932, **65**, *B*, 457.
[9] Parker, *ibid.*, 1890, **23**, 1845.
[10] Boeseken and Koning, *Rec. Trav. chim.*, 1911, **30**, 130.
[11] Fries and Vogt, *Annalen*, 1911, **381**, 343.
[12] Zincke and Lenhardt, *ibid.*, 1913, **400**, 14.
[13] Fichter and Wenk, *Ber.*, 1912, **45**, 1379.

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or by oxidation with nitric acid, it had m. p. 208—210°]. *p*-Nitrobenzyl *p*-nitrophenyl sulphone, yellow needles, m. p. 195° (cf. ref. 15), from ethanol–dioxan (2 : 1).

o-*Nitrophenyl phenyl sulphoxide*. Chloroform solutions of perbenzoic acid (4·12%; 144 c.c.) and *o*-nitrophenyl phenyl sulphide (10 g. in 150 c.c.) were mixed and cooled in ice. Next day, the mixture was washed with 5% aqueous sodium carbonate, dried, and evaporated. The *sulphoxide*, yellow needles, had m. p. 92—93° (from ligroin) (Found: N, 5·8. $C_{12}H_9O_3NS$ requires N, 5·7%).

m-*Nitrophenyl phenyl sulphoxide*, prepared as the *ortho*-isomer, gave needles, m. p. 76—77° (from benzene–ligroin) (Found: N, 5·7%).

p-Nitrophenyl phenyl sulphone was prepared by oxidation of the sulphide with peracetic acid at 100° as plates, m. p. 172—173° (Fromm and Wittmann,[14] by oxidation with chromic acid, obtained material m. p. 169° and 172°).

Benzyl *p*-nitrobenzyl sulphone was prepared as described above. The crude product gives ivory-coloured plates, m. p. 209° (as in the literature [15]) from ethanol–dioxan (2 : 1).

We thank Professor C. K. Ingold, F.R.S., for helpful discussions, and Dr. Tundo for co-operation in the preparation of some compounds. We acknowledge financial support from the Italian "Consiglio Nazionale Ricerche."

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[14] Fromm and Wittmann, *Ber.*, 1908, **41**, 2270.
[15] Waldron and Reid, *J. Amer. Chem. Soc.*, 1923, **45**, 2399.

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263. *Ionophoresis of Carbohydrates. Part V.* Reaction of the Methyl Fructofuranosides and Fructopyranosides, and of Related Compounds, with Borate Ions.*

By A. B. FOSTER.

The reaction of a series of glycofuranosides and glycopyranosides with borate ions has been measured. The structures of the methyl α- and β-D-fructofuranoside and methyl α- and β-D-fructopyranoside allocated on the basis of borate-ion interactions (M_G values) correspond with those allocated on the basis of specific optical rotations.

INFORMATION on the structure of carbohydrates has been gained in certain instances [1,2] by observing their reaction with borate ions in alkaline media. The reaction of carbohydrates with borate ions in aqueous boric acid at pH 5 has been extensively studied by Böeseken [3] using conductimetric methods. However, in alkaline media, borate-ion interactions are intensified [4] and new types of interactions have been observed.[5] The M_G value [1] has been adopted in these investigations as a convenient index of borate-ion interaction: it may be determined for a given substance by zone electrophoresis [6] (ionophoresis) on paper by using the enclosed-strip technique.[7]

Recent chromatographic techniques [8,9] have made available a number of new methyl glycofuranosides and through the courtesy of Professor E. Berner samples have been made available for ionophoresis.

* Part IV, *J.*, 1956, 4311.

[1] Foster, *J.*, 1953, 982.
[2] (*a*) Foster and Stacey, *Chem. and Ind.*, 1953, 279; (*b*) Foster, *ibid.*, 1953, 591; (*c*) Foster, Overend, Stacey, and Vaughan, *J.*, 1953, 3308; (*d*) Bera, Foster, and Stacey, *J.*, 1956, 4531.
[3] Böeseken, *Adv. Carbohydrate Chem.*, 1949, **4**, 189.
[4] Consden and Stanier, *Nature*, 1952, **169**, 783.
[5] See, *e.g.*, Foster and Stacey, *J.*, 1955, 1778.
[6] Flodin and Tiselius, *Adv. Protein Chem.*, 1953, **8**, 46.
[7] Foster, *Chem. and Ind.*, 1952, 1050.
[8] Augestad, Berner, and Weigner, *ibid.*, 1953, 376.
[9] Augestad and Berner, *Acta Chem. Scand.*, 1954, **8**, 251.

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From the M_G values recorded in the Table it is seen that both methyl α- and β-D-arabofuranoside have a definite though a very weak reaction with borate ions. Three possibilities exist, in these glycofuranosides, for borate-ion interactions, involving the 2 : 3-, 2 : 5-, and 3 : 5-hydroxyl groups. (The relative stereochemical disposition of all three hydroxyl groups precludes the formation of a " tridentate " complex.[10]) The 2 : 3-hydroxyl groups are *trans*-related and are effectively fixed in space because they are attached to the almost completely rigid furan ring;[11] the O–O distance is greater than that in *cyclo*hexane-*trans*-1 : 2-diol which does not react with borate ions.[2b] A seven-membered ring would result from a borate-ion reaction with the 2 : 5-hydroxyl groups and the formation of such a complex would seem unlikely since butane-1 : 4-diol, which would yield a similar complex, has a zero M_G value.[12] The formation of a borate complex spanning the 3 : 5-hydroxyl groups would necessitate the formation of a somewhat distorted six-membered ring and would seem to be the most likely of the three possibilities considered. Evidence which supports this view is the observed [13] small, but definite, difference in M_G values of adenosine-2′ and -3′ phosphate (1·06 and 1·02 respectively) which could be due to the former's acquiring extra negative charge by reaction of borate ions with the 3′ : 5′-hydroxyl groups. It is of interest that the weak reaction of structures of the type (I) and (II) with borate ions has been of value [2d] in the determination of the structure of 2 : 5-anhydro-D-mannitol.

cis-Arrangement of the hydroxymethyl and vicinal hydroxyl group as in methyl α- and β-D-xylofuranoside permits a much stronger reaction with borate ions, as indicated by the M_G values in the Table. The M_G values of methyl α- and β-D-fructofuranoside (0·60 and 0·04 respectively) are consistent with the presence of, respectively, vicinal *cis*- and *trans*-related hydroxymethyl and hydroxyl groups at positions 2 and 3, *i.e.*, the compounds have the structures (V) and (VI).

Thus the structures allocated to the fructofuranosides on the basis of their M_G values are in agreement with those allocated on the basis of specific optical rotations (cf. Pigman and Goepp [14]).

The M_G values of the D-gluco- and D-galacto-furanoside derivatives in the Table show, as expected, a stronger reaction with borate ions in the former series where the non-protonic groups on $C_{(3)}$ and $C_{(5)}$ are *cis*-related (cf. McPherson and Percival's observations [15] on the influence of these furanosides on the conductivity of boric acid). The M_G values of the D-galactofuranose derivatives are higher than would be expected from the fact that

M_G values of some glycofuranosides and pyranosides.

	M_G value		M_G value
Me α-D-arabofuranoside (I)	0·035	Me α-D-galactofuranoside	0·41
Me β-D-arabofuranoside (II)	0·035	Me β-D-galactofuranoside	0·31
Me α-D-xylofuranoside (III)	0·56	1 : 4-Anhydro-D-galactitol	0·47
Me β-D-xylofuranoside (IV)	0·33	Me α-D-fructopyranoside [c] (VII)	0·71
Me α-D-fructofuranoside [a] (V)	0·60	Me β-D-fructopyranoside [d] (VIII)	0·59
Me β-D-fructofuranoside [b] (VI)	0·04	Me α-D-mannopyranoside (IX)	0·42
Me α-D-glucofuranoside	0·73	Me β-D-gulopyranoside (X)	0·72
1 : 2-*O*-*iso*Propylidene-α-D-glucofuranose	0·73		

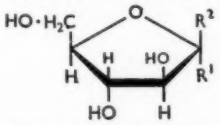
Physical constants of the fructose derivatives (personal communication from Professor E. Berner): (*a*) m. p. 81°, $[\alpha]_D$ +93° in H_2O; (*b*) syrup, $[\alpha]_D$ −48° in H_2O; (*c*) syrup, $[\alpha]_D$ +80° in EtOH; (*d*) m. p. 120°, $[\alpha]_D$ −173° in H_2O.

propane-1 : 2-diol has an M_G value of 0·2 and the assumption that only the 5 : 6-hydroxyl groups in these derivatives react with borate ions. Other, as yet undefined, borate-ion interactions appear to be operating here.

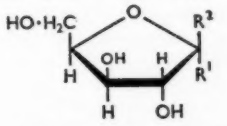
Because of a lack of suitable compounds it has not been possible to measure directly

[10] Angyal and McHugh, *Chem. and Ind.*, 1956, 1147.
[11] Mills, *Adv. Carbohydrate Chem.*, 1955, **10**, 1.
[12] Frahn and Mills, *Chem. and Ind.*, 1956, 578.
[13] Burke and Foster, *ibid.*, 1955, 94.
[14] Pigman and Goepp, " Carbohydrate Chemistry," Academic Press, New York, 1948, p. 80.
[15] Macpherson and Percival, *J.*, 1937, 1920.

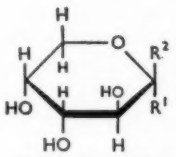
the reaction of borate ions with vicinal *cis*-related hydroxyl and hydroxymethyl groups in pyran derivatives but it may be deduced that they react more strongly than with the corresponding *trans*-related groups. (The reaction of the latter grouping with borate ions has been noted in Part II of this series.) Thus borate ions may react separately at two points in methyl β-D-gulopyranoside (X) and methyl α-D-mannopyranoside (IX), *viz.*, the



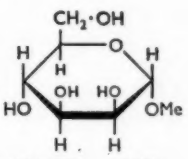
(I) R^1 = OMe, R^2 = H
(II) R^1 = H, R^2 = OMe
(V) R^1 = OMe, R^2 = CH_2·OH
(VI) R^1 = CH_2·OH, R^2 = OMe



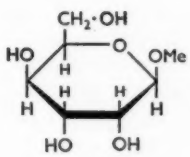
(III) R^1 = OMe, R^2 = H
(IV) R^1 = H, R^2 = OMe



(VII) R^1 = OMe, R^2 = CH_2·OH
(VIII) R^1 = CH_2·OH, R^2 = OMe



(IX)



(X)

cis-2 : 3-hydroxyl groups, and the hydroxymethyl and 4-hydroxyl groups which are *trans*-related in the latter and *cis*-related in the former. On the reasonable assumption that the contribution to the negative charge of the derivatives (IX) and (X) conferred by reaction of the 2 : 3-hydroxyl groups with borate ions is similar, the much greater M_G value of the D-gulose derivative (X) (see Table) probably originates in a readier reaction of the 4 : 6-hydroxyl groups with borate ions in this than in the D-mannose derivative (IX). Although the reaction of the 4 : 6-hydroxyl groups in the D-mannose derivative (IX) is sterically hindered by the glycosidic methoxyl group (Part II) this can account for only a fraction of the difference in the M_G values of methyl α-D-mannopyranoside and β-D-gulopyranoside.

The higher M_G value of methyl α-D-fructopyranoside (VII) than of the β-anomer (VIII) is consistent with the presence of respectively *cis*- and *trans*-related 3-hydroxyl and 2-hydroxymethyl groups in the two compounds. It is of interest that methyl β-D-gulopyranoside (X) and α-D-fructopyranoside (VII) which have closely related structures, with respect to the steric disposition of their hydroxyl groups, also have closely similar M_G values.

From a knowledge of the M_G values of the methyl D-fructofuranosides (V) and (VI) the observed low M_G value (< 0.05) for inulin is not unexpected. A similar low M_G value would be predicted for levan.

Experimental

The apparatus and technique employed in ionophoresis have been previously described.[7] Ionophoreses were performed on Whatman No. 3 paper in sodium borate [16] at pH 10 under potential gradients of 20—40 v/cm. Non-reducing carbohydrates were detected by means of ammoniacal silver nitrate.[17]

Acknowledgment is made to Professor M. Stacey, F.R.S., for his interest, to Professor E. Berner for generously providing the furanoside and fructopyranoside derivatives, and to Dr. H. G. Fletcher, jun., for a sample of 1 : 4-anhydro-D-galactitol.

Chemistry Department, The University,
Edgbaston, Birmingham, 15. [*Received, October 10th*, 1956.]

[16] Foster, Newton-Hearn, and Stacey, *J.*, 1956, 30.
[17] Hough, *Nature*, 1950, **165**, 400.

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264. *Peptides. Part VI.* Further Studies of the Synthesis of Peptides through Anhydrides of Sulphuric Acid.*

By D. W. Clayton, J. A. Farrington, G. W. Kenner, and J. M. Turner.

Various improvements in the method described previously [1] are recorded. The extent of racemisation during the condensation of benzyloxycarbonylglycyl-L-alanine with L-phenylalanylglycine has been studied by separating any DL-diastereoisomer from the main product. In this instance racemisation can be very nearly excluded if the coupling is carried out in aqueous dimethylformamide buffered with magnesium carbonate. No racemisation could be detected when the ethyl ester of L-phenylalanylglycine was acylated in anhydrous dimethylformamide.

Part I of this series [1] contained a method for condensing the carboxyl group of an *N*-acylamino-acid or -peptide with the amino-group of another amino-acid or peptide. The three steps of the process are preparation of an anhydrous dimethylformamide solution of a salt of the carboxylic acid, reaction between the salt and a solution of sulphur trioxide in dimethylformamide, and coupling of the resultant mixed anhydride † (I) with the amino-compound. We now report closer examinations of each step and of the retention of configuration during the whole process.

The earlier work was carried out with potassium salts or, when these were insufficiently soluble, with trimethylphenylammonium salts. During the drying of the dimethylformamide solutions by fractional vacuum-distillation at about 50° there is some decomposition of the latter salts to dimethylaniline and the methyl ester of the carboxylic acid. We have not tried other quaternary ammonium salts which would be less prone to this side-reaction, because the lithium salts have proved perfectly satisfactory. Even when crystallisation has occurred, the lithium salts have been sufficiently soluble for convenient drying and reaction with the sulphur trioxide solution. It is noteworthy that the hitherto uncrystallised benzyloxycarbonyl-L-leucine gives a crystalline lithium salt.

A drawback of the original method was its need of anhydrous sulphur trioxide. However, sulphur trioxide prepared simply by distillation of oleum gives equally good results if the co-ordination compound with dimethylformamide ($^-SO_3{\cdot}O{\cdot}CH{:}NMe_2^+$) is allowed to crystallise at −40° before being redissolved in pure dimethylformamide. The solution is unaffected by storage at −40° for two months, but decomposes slowly at 0°. It gives 95—97% yields in the condensation of toluene-*p*-sulphonylglycine with *cyclo*hexylamine, but the *cyclo*hexylamides of benzyloxycarbonyl-glycine, -glycylglycine, and -glycylphenylalanine are formed in no more than 88% yield. We attribute this difference to

$$NH_2R' + \underset{(I)}{R{\cdot}CO{\cdot}O{\cdot}SO_3^-} \longrightarrow \begin{cases} \rightarrow R{\cdot}CO{\cdot}NHR' \\ \rightarrow {}^-SO_3{\cdot}NHR' \text{ (II)} \end{cases}$$

competitive formation of the sulphamate (II); although there is no close analogy, this assumption is in line with the results of work with mixed carboxylic anhydrides.[3] Similar or slightly lower yields were obtained when the esters of amino-acids or peptides were used instead of *cyclo*hexylamine; in these instances an equivalent amount of triethylamine was also added in order to neutralise the liberated lithium hydrogen sulphate.

An unusual feature of the original method was that coupling of the mixed anhydrides

* Part V, *J.*, 1956, 371.

† The acylating reagent might be the cation $R{\cdot}CO{\cdot}O{\cdot}CH{:}NMe_2^+$, derived by ejection of sulphate ion instead of dimethylformamide from the sulphur trioxide–dimethylformamide complex. We regard the mixed anhydride as more likely in analogy with the known acetylsulphuric acid [2] and the numerous peptide syntheses involving mixed anhydrides, but an attempt to isolate a mixed anhydride from the dimethylformamide solution was unsuccessful.

[1] Kenner and Stedman, *J.*, 1952, 2069.
[2] Van Peski, *Rec. Trav. chim.*, 1921, **40**, 103.
[3] Wieland and Stimming, *Annalen*, 1953, **579**, 97.

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(I) with amines was carried out in aqueous solution; this permitted the acylation of free amino-acids or peptides, instead of their esters, and consequent simplification of the synthesis. The acyl sulphates (I) are fortunately not only soluble in water but also surprisingly stable to hydrolysis by water and, to a smaller extent, hydroxyl ions; the half-life of lithium benzyloxycarbonylglycyl sulphate was estimated to be 10 hr. at pH 6·7 and 1 hr. at pH 9. In selecting a pH for the coupling, a balance has to be struck between the advantages of a low value in avoiding hydroxyl ions and of a high one in liberating the amino-groups from the ammonium form. In reactions between trimethylphenylammonium toluene-*p*-sulphonylglycyl sulphate and phenylalanine or phenylalanylglycine, the optimum pH appears to be near the p*K* of the ammonium ions. The yields fall off more sharply above the optimum pH than below it and they are higher, particularly at the lower pH's, with the dipeptide (p*K* 7·71)[4] than with the amino-acid (p*K* 9·13).[4]* We refrain from detailed discussion of these results for three reasons: the reactions were carried out under preparative conditions, and neither the composition of the medium nor the pH was constant; trimethylphenylammonium toluene-*p*-sulphonylglycyl sulphate is not a typical anhydride, for, as already mentioned, it gives higher yields under anhydrous conditions than do other acyl sulphates; the pH must in any case be kept below the optimum value in order to avoid serious racemisation (see next paragraph). A generally convenient and satisfactory technique is to add the dimethylformamide solution of the anhydride (I) to an aqueous solution of the amino-compound, buffered to about pH 6·8 with powdered magnesium carbonate. Our earlier work was done with much cruder technique and an unsatisfactory coupling of benzyloxycarbonyl-L-phenylalanine with glycine was recorded;[1] no such difficulty was encountered during a repetition under better controlled conditions. Holley and Holley[6] have shown that the long known[7] benzyloxycarbonyl-L-phenylalanine, m. p. 128°, has a neutralisation equivalent of 370 instead of 299, and they obtained an oil with an equivalent of 310. By counter-current distribution we have isolated material with m. p. 87° and equivalent 298.

Racemisation of the asymmetric centre next to the active carbonyl group is possible during any peptide synthesis of the mixed anhydride type, but the risk is very small for the anhydrides of the benzyloxycarbonyl, toluene-*p*-sulphonyl, or phthaloyl derivatives of amino-acids. The condensation of benzyloxycarbonylglycyl-L-phenylalanine with glycine was examined in our earlier work[1] and it was satisfactory. Re-investigation confirmed this when the pH of the coupling was controlled with phenol-red as indicator between 7·4 and 8·5, but there was much racemisation during control with phenolphthalein. These results were obtained by determining the optical rotation of the crude tripeptide derivative, because crystallisation could have removed some of the D-isomer. A better method was needed for a closer study of the phenomenon. Enzymic tests[8] could have been used, but it seemed simpler to arrange that racemisation would produce a diastereoisomer, separable from the main product. A suitable example was found in the coupling of benzyloxycarbonylglycylalanine with phenylalanylglycine. The mixture of tetrapeptide derivatives produced from the two DL-components was resolved by an extended counter-current distribution between ethyl acetate and a phosphate buffer, and the proportions in the mixture could, of course, be calculated accurately from the distribution curve.†

* An explanation of this difference is provided by the accurate investigation[5] of the analogous reaction between carbon disulphide and amino-acids or peptides. The weaker bases have, as expected, lower specific rates of reaction, but this effect is more than counterbalanced by the larger concentrations of free amino-groups.

† A spectrophotometric method, based on the iodate–iodide reaction, was developed for estimating the concentration of acid in the ethyl acetate. This was convenient for following the progress of a distribution, because negligible amounts of solution were removed for analysis. The more reliable method of weighing the residues after evaporation was used when precision was needed.

[4] Cohn and Edsall, "Proteins, Amino Acids and Peptides," Reinhold, New York, 1943, p. 84.
[5] Léonis, *Compt. rend. Trav. Lab. Carlsberg*, 1949, **26**, 315.
[6] Holley and Holley, *J. Amer. Chem. Soc.*, 1952, **74**, 3074.
[7] Bergmann, Zervas, Rinke, and Schleich, *Z. physiol. Chem.*, 1934, **224**, 36.
[8] Cf. Greenstein, *Adv. Protein Chem.*, 1954, **9**, 187.

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It is worth noting that three parts of the LL-DD racemate were produced for every two parts of the LD-DL racemate. For the actual test runs assuredly pure samples of the two L-reagents were required. Small amounts of benzyloxycarbonylglycyl-DL-alanine (m. p. 183°) are easily detected in the L-isomer (m. p. 133°). The purity of our L-phenylalanylglycine was checked by solubility analysis [9] since there is disagreement in the literature [10] about its optical rotation. To our disappointment, coupling of the two L-reagents at about pH 8 gave one part of DL-tetrapeptide derivative for every six parts of the LL-form, although the amount of racemisation during the preparation of benzyloxycarbonylglycyl-L-phenylalanylglycine under similar conditions must have been smaller. However, when the pH was kept below 6·8 by powdered magnesium carbonate, the amount of DL-diastereoisomer was not detectable from the distribution curve; the minute amount of material recovered from the position expected for the DL-diastereoisomer must have been a mixture for it had a rotation of about −18° instead of +15°. It must have been mainly LL (rotation −31°) and less than 1% of the product can have been the DL-form. The difference between the behaviours of these two coupling reactions emphasises the danger of generalising without wide experience, but it is reasonable to expect an acceptably small amount of racemisation during most other couplings buffered with magnesium carbonate. The risk of racemisation will probably be greater when the coupling reaction is slower and the life of the anhydride is longer.

Racemisation through removal of a proton from the α-position of a mixed anhydride should be hindered by the absence of water. In fact we have been unable to detect it at all during the reactions, in anhydrous dimethylformamide, of the sulphuric anhydrides of benzyloxycarbonylglycyl-L-phenylalanine and benzyloxycarbonylglycyl-L-alanine with the ethyl esters of glycine and L-phenylalanylglycine respectively. Anderson, Blodinger, and Welcher [11] have shown that quite small amounts of benzyloxycarbonylglycyl-DL-phenylalanylglycine ethyl ester crystallise from ethanolic solution in preference to the L-isomer, but only the latter crystallised in our experiment. The second example is regarded by us as a stricter test both because, judged from our experience of the couplings in aqueous solution, the chance of racemisation is greater and the efficiency of detection, through alkaline hydrolysis followed by counter-current distribution, is superior.

Most of our work has been done with peptides derived from simple amino-acids, but some miscellaneous experiments with cystine, *S*-benzylcysteine, serine, tyrosine, and tryptophan are also recorded. These show that the phenolic hydroxyl group of tyrosine needs protection when it is part of the mixed anhydride, but the indole nucleus of tryptophan is unaffected.

Our conclusions are that the sulphuric anhydride method is an efficient means of acylating the esters of amino-acids and peptides in anhydrous dimethylformamide; it has the advantage over most other methods of the mixed-anhydride type that the by-product, in this instance a sulphamic acid, can be extracted easily. The method is also useful for acylating the amino-acids and peptides themselves in aqueous media buffered with magnesium carbonate, but there is a greater, although by no means excessive, risk of racemisation under these conditions; the merit of this more direct route has been discussed elsewhere.[1, 12]

Experimental

M. p.s are corrected. Analytical samples were dried for 6 hr. at 80°/1 mm. over phosphoric oxide. Evaporations were carried out under reduced pressure.

Spectrophotometric Estimation of Microgram Quantities of Carboxylic Acids Dissolved in Ethyl Acetate.—Potassium iodide (5 g.; "AnalaR") and potassium iodate (0·1 g.; "AnalaR")

[9] Mader, "Organic Analysis," Interscience Pub., Inc., New York, 1954, Vol. II, p. 253; Williams and Young, *J.*, 1951, 1745.

[10] Fischer and Schoeller, *Annalen*, 1907, **357**, 19; Sheehan, Chapman, and Roth, *J. Amer. Chem. Soc.*, 1952, **74**, 3825; Vaughan and Eichler, *ibid.*, 1953, **75**, 5559.

[11] Anderson, Blodinger, and Welcher, *J. Amer. Chem. Soc.*, 1952, **74**, 5309.

[12] Kenner, *Chem. Soc. Special Publ.*, No. 2, 1955, p. 103.

were dissolved in water (100 c.c.), which had been distilled in glass and freed from carbon dioxide by having had nitrogen slowly bubbled through it for not less than ½ hr. An ample quantity of this solution, which kept better in bulk, was made immediately before a series of estimations. The optical density of 2·5 c.c. of the solution, which was below 0·2, was measured in a 1 cm. cuvette at 355 mμ,[13] and then an accurately measured volume (between 0·01 and 0·15 c.c.) of the ethyl acetate solution was added to the cuvette. The solution was agitated for 15 sec. with a square-headed glass stirrer before the optical density was measured again. A calibration run with benzyloxycarbonylglycine showed the expected linear relation between the increase in optical density (ΔD) and volume of added solution with $\Delta D = 1$ corresponding to 0·425 microequivalent of acid. During a series of determinations the cuvette was not washed out but the syringe was flooded twice with the solution before the aliquot sample was ejected. Ethyl acetate which had been washed with sodium hydrogen carbonate solution and distilled gave a negligible ΔD, but after several hours, particularly during counter-current distribution, acetic acid could be detected.

Counter-current Distribution.—The partition coefficients varied slightly in different runs, because the room was not thermostatically controlled. Unless otherwise specified, the solvent system was ethyl acetate (fractionally distilled) and M-phosphate buffer, made from the appropriate amounts of KH_2PO_4 and K_2HPO_4. Before use the two phases were shaken together at the temperature of distribution and, as an additional surety of equilibrium, solute was not added to the first tube. Instead, the solute was dissolved in ethyl acetate and added to the second tube (tube 0) and sometimes two or four more. For all the long distributions a fully automatic glass 100-tube apparatus holding 20·5 c.c. of each phase was used; the settling time was variable, 5 min. being usual. At the end the peptide derivatives were driven into the ethyl acetate by addition of either syrupy phosphoric acid (1 c.c. for every 20 c.c. of buffer) or concentrated hydrochloric acid [for every 20 c.c. of buffer containing $(10 - x)$ parts of KH_2PO_4 to x of K_2HPO_4, $(3 + x)/6$ c.c.]. A second equal volume of ethyl acetate was used to complete the extraction. The bulk of the ethyl acetate was evaporated and the remainder was pipetted from any salts which crystallised. The remaining solvent was evaporated and crystallisation of the peptide derivative was encouraged. Finally, dry air was blown through the flask until its weight was constant.

Calculation of Counter-current Distribution Curves.—The partition coefficient, K, was derived from the position of the peak in tube $r_{max.}$ and the relation $K = (r_{max.} + 0{\cdot}5)/(n - r_{max.} + 0{\cdot}5)$, where n is the number of transfers and the tubes are numbered from 0 to n with appropriate additions for recycling distributions. For large numbers of transfers the amount of material Y, in a tube lying at a distance x from tube $r_{max.}$, which contained Y_0, was calculated from $Y/Y_0 = \exp(-x^2/p)$, where $p = 2nK/(K + 1)^2$. When the material had originally been added to the first three tubes, the values of Y calculated as above for single-tube filling were multiplied by $(1 - 2/3p + 4x^2/3p^2)$. For five-tube filling the factor was $(1 - 2/p + 1{\cdot}6/p^2 + 4x^2/p^3 - 4{\cdot}8x^2/p^3)$. When the spectrophotometric estimation was applied to a long distribution, a small base-line reading, caused by acetic acid, was deducted from the values of ΔD.

Anhydrous Dimethylformamide.—This was the residue after traces of moisture had been stripped, by fractionation at 15 mm. through a 6″ column packed with steel gauze,[14] from commercial material which had been fractionally distilled after being mixed with benzene.

Dimethylformamide Solution of Sulphur Trioxide–Dimethylformamide Complex.—Oleum (100 c.c. of 60%) was heated by a mantle at 110° under a 6 × 1″ column packed with Fenske glass helices, while nitrogen was bubbled through it. The receiver was cooled in ice and guarded with a tube of phosphoric oxide. Distillation was stopped when about 30 g. of sulphur trioxide had collected, and most of this was then distilled by gentle warming into a bulb fitted with a tail-joint. The bulb was then immediately attached to a three-necked flask, fitted with a stirrer and guard-tube and containing 85 c.c. of anhydrous dimethylformamide. The flask was cooled to −15° and the bulb was warmed gently so that sulphur trioxide distilled over the surface of the dimethylformamide. Like the previous transfer, this was interrupted when oily droplets were seen in the residue; about 21 g. of sulphur trioxide were added. The flask was kept for 2 hr. between −40° and −60° before the yellow liquor was sucked off through a sintered-glass filter-stick. The colourless crystals were washed with anhydrous dimethylformamide (10 c.c.) before being dissolved in 200 c.c. The solution (approx. M) was kept at −40° in a flask, the

[13] Cf. Custer and Natelson, *Analyt. Chem.*, 1949, **21**, 1005.
[14] Dixon, *J. Soc. Chem. Ind.*, 1949, **68**, 88.

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stopper of which was surrounded by air dried with phosphoric oxide. The strength of this solution was determined by titration with alkali and its quality by the yield of toluene-*p*-sulphonylglycine *cyclo*hexylamide, which was between 93 and 97%. Storage for one month at −5° caused 3% drop in the yield, but deterioration at −40° was considerably slower.

Preparation of the Mixed Anhydrides.—The exact volume of sulphur trioxide solution, required according to the alkaline titration, was pipetted into the ice-cooled solution of the carboxylate salt.[15] Occasionally this had crystallised during the drying, but it quickly dissolved in presence of the sulphur trioxide solution.

In several runs about 5% of *toluene*-p-*sulphonylglycine methyl ester*, m. p. 90° (Found: C, 49·5; H, 4·9; N, 6·0. $C_{10}H_{13}O_4NS$ requires C, 49·4; H, 5·4; N, 5·8%), identified by comparison with material prepared with diazomethane, was produced from the trimethylphenylammonium salt of toluene-*p*-sulphonylglycine. Decomposition of the salt of phthaloyl-DL-phenylalanine was more rapid and 78% of the *methyl ester*, m. p. 87—88° (Found: C, 70·3; H, 4·6; N, 4·5. $C_{18}H_{15}O_4N$ requires C, 69·9; H, 4·9; N, 4·5%), was produced in 20 hr.

Toluene-p-*sulphonylglycine* cyclo*Hexylamide.*—*cyclo*Hexylamine (3 c.c., 25 mmoles) was added to a solution of the lithium, potassium, or trimethylphenylammonium salt of toluene-*p*-sulphonylglycylsulphuric acid (2 mmoles) in dimethylformamide (30 c.c.) at 0°. The solution was kept at 20° for 30 min. before evaporation. The residue was partitioned between ethyl acetate (40 c.c.) and 3N-sulphuric acid, which was extracted twice more with ethyl acetate. The combined ethyl acetate extracts (120 c.c.) were washed with saturated sodium hydrogen carbonate solution (3 × 10 c.c.) and water (10 c.c.). The aqueous washings were re-extracted with ethyl acetate (40 c.c.) before being acidified with hydrochloric acid and extracted with ethyl acetate (5 × 40 c.c.). Crystalline toluene-*p*-sulphonylglycine was recovered by evaporation and was dried to constant weight in a current of air. Similarly, the *cyclo*hexylamide (*ca.* 95%) was obtained from the earlier extracts. The total weight of air-dried materials corresponded to *ca.* 2·02 mmoles. The cyclo*hexylamide* was recrystallised from benzene–light petroleum (b. p. 40—60°) and had m. p. 113·5—115° (Found: C, 58·0; H, 7·2; N, 8·7. $C_{15}H_{22}O_3N_2S$ requires C, 58·0; H, 7·2; N, 9·0%).

Benzyloxycarbonylglycylglycine cyclo*Hexylamide.*—Prepared in the same way as the foregoing compound (yield 88%; 13% of starting material recovered), this *compound* recrystallised from methanol in needles, m. p. 173° (Found: C, 62·3; H, 7·3; N, 12·1. $C_{18}H_{25}O_4N_3$ requires C, 62·2; H, 7·3; N, 12·1%). Benzyloxycarbonylglycine *cyclo*hexylamide[16] was prepared likewise.

Benzyloxycarbonylglycyl-DL-*phenylalanine* cyclo*Hexylamide.*—This preparation was like the foregoing ones except that considerably more ethyl acetate was needed to dissolve the cyclo*hexylamide*, which, recrystallised from ethyl acetate, had m. p. 189° (Found: C, 68·6; H, 7·2; N, 9·6. $C_{25}H_{31}O_4N_3$ requires C, 68·6; H, 7·1; N, 9·6%).

General Procedures of Coupling the Mixed Anhydrides with Amines.—(a) *In water buffered with magnesium carbonate.* The ice-cooled dimethylformamide solution of the mixed anhydride (5—10 c.c. per mmole) and then magnesium carbonate (0·2 g. for each mmole) were added to a stirred solution of the amino-acid or peptide (equivalent to the anhydride) in a convenient volume of water. Stirring was continued for 15 hr. while the pH rose rapidly to 6·7 and finally to about 7·5. The excess of carbonate was dissolved with hydrochloric acid (pH 5), and the solvents were then evaporated. The peptide derivative was obtained by thorough partition between ethyl acetate and 3N-sulphuric acid, followed by evaporation of the ethyl acetate.

(b) *In dilute sodium hydroxide.* An aqueous solution of the amino-acid or peptide together with an indicator was magnetically stirred. An ice-cooled solution of the mixed anhydride in dimethylformamide was forced during *ca.* 15 min. by pressure of dry nitrogen to drop on to the surface of the aqueous solution, while N-sodium hydroxide was added so as to maintain the indicator colour (matched with a standard). The tip of the delivery tube was kept in an atmosphere of dry nitrogen. The mixture was stirred for 15 min. further. It was then brought to pH 5 and worked up as in (a). As the dimethylformamide content of the solution increased, the pH tended to rise and the approximate extent of this rise was determined with a glass electrode in a blank experiment with glycine. The indicators used and the respective initial and approximate final pH's were bromocresol-purple (6·0—6·05), bromothymol-blue (7·0—8·2),

[15] Kenner and Stedman, *J.*, 1952, 2072.
[16] Clayton, Kenner, and Sheppard, *J.*, 1956, 375.

phenol-red (7·5—8·5), *m*-cresol-purple (8·0—9·0), thymol-blue (8·7—10·0), phenolphthalein (9·0—*ca.* 12·0), and thymolphthalein (10·0—*ca.* 12·3).

(c) *In anhydrous dimethylformamide.* Triethylamine (2 equivs.) was added to a solution of either the hydrochloride or the hydrobromide of the amino-compound in anhydrous dimethylformamide. This mixture was added to the ice-cooled mixed anhydride, and the whole was kept at 20° for 1 hr. A little water was added and the pH was brought to 5 with N-sulphuric acid. The solvents were evaporated and the residue was partitioned between ethyl acetate and 3N-sulphuric acid. The neutral product and the recovered acid were then isolated in the usual way (see above). They accounted for all the anhydride used.

Benzyloxycarbonylglycylglycine.—Method (b) with phenolphthalein yielded 81% of material, m. p. 178°. Most of the product remained undissolved in the ethyl acetate and sulphuric acid.

Benzyloxycarbonylglycylglycine Ethyl Ester.—Method (c) yielded 85% and m. p. 77·5° after crystallisation from benzene–light petroleum (b. p. 60—80°).

Benzyloxycarbonylglycylglycylglycine.—Method (b) with thymol-blue yielded 75% of material, which had been recrystallised from water and had m. p. 196°. Most of the crude product crystallised directly from the acid and ethyl acetate, and the remainder was recovered by butan-1-ol extraction of the acidic liquors (total 84%).

Benzyloxycarbonylglycyl-L-alanine.—Method (b) with phenol-red gave 87% of product and 13% of benzyloxycarbonylglycine, separated by a 96-transfer distribution with 0·9M-KH_2PO_4/0·1M-K_2HPO_4 and recovered from tubes 10—45 and 48—70 respectively. The peak corresponding to the product had a steep leading edge and broad summit; three 20·5 c.c. tubes had been filled originally. The product was recrystallised from ethyl acetate and had m. p. 133°, $[\alpha]_D^{19}$ −9·5° (±0·2°) (*c* 4·4 in EtOH). This compound is evidently dimorphic.[17]

Method (a) yielded 61% of material, m. p. 124—126°, without counter-current distribution.

Benzyloxycarbonylglycyl-DL-alanine.—Method (b) with phenolphthalein gave 75% of material, m. p. 181° raised to 183° by recrystallisation from methanol. Most of this crystallised from the ethyl acetate and acid.

Benzyloxycarbonyl-L-leucylglycine.—Method (b) with thymol-blue yielded 64% of material, m. p. 118°, isolated from tubes 3—6 of a 10-transfer distribution with 0·5M-KH_2PO_4/0·5M-K_2HPO_4.

Benzyloxycarbonyl-L-leucylglycine Ethyl Ester.—Method (c) yielded 85% of ester, m. p. 103—104°.

Benzyloxycarbonyl-DL-leucylglycine Ethyl Ester.—Method (c) yielded 87% of *ester*, which was recrystallised from aqueous ethanol and had m. p. 91° (Found, in material dried at 40°: C, 61·9; H, 7·4; N, 8·0. $C_{18}H_{26}O_5N_2$ requires C, 61·7; H, 7·5; N, 8·0%).

Benzyloxycarbonylglycyl-DL-leucylglycine.—Hydrogen was bubbled for 3 hr. through a stirred solution of the foregoing ester (6·24 g., 20 mmoles) in ethanol (100 c.c.) and concentrated hydrochloric acid (2 c.c.) containing a mixture of platinum and palladium oxide catalysts. Evaporation of the liquor gave an oil, which was dried by repeated evaporation with anhydrous dimethylformamide and then coupled with benzyloxycarbonylglycine (20 mmoles) by method (c). The neutral product (5·7 g.) did not crystallise. It was treated with dioxan (50 c.c.) and N-sodium hydroxide (15 c.c.) for 5 hr. at 20°. The acidic product of this hydrolysis was subjected to a 9-transfer distribution with 0·8M-KH_2PO_4/0·2M-K_2HPO_4. The *benzyloxycarbonyltripeptide* (4·22 g., 60% overall yield) was recovered from tubes 0—5 and, recrystallised from aqueous ethanol, had m. p. 161° (Found: C, 57·2; H, 6·7; N, 11·1. $C_{18}H_{25}O_6N_3$ requires C, 57·0; H, 6·6; N, 11·1%). Subsequent preparations could be crystallised without counter-current distribution.

Benzyloxycarbonylglycyl-L-leucylglycine Ethyl Ester.—Benzyloxycarbonyl-L-leucylglycine ethyl ester was hydrogenated and then coupled with benzyloxycarbonylglycine in the same fashion as in the DL-series. The yield was 78% of product, having m. p. 109°[18] after recrystallisation from aqueous ethanol.

Benzyloxycarbonyl-L-phenylalanine.—Material prepared in the ordinary way was recrystallised from benzene and had m. p. 122—124°, $[\alpha]_D^{14}$ +4·8° (±0·2°) (*c* 4·4 in acetic acid), neutralisation equivalent 358, in agreement with published data.[6,7] An 8-transfer distribution with 0·075M-KH_2PO_4/0·425M-K_2HPO_4 showed a peak with K 1·81. From tubes 3—7 65% of crystalline material, very soluble in benzene were obtained. Recrystallised from ethyl acetate,

[17] Erlanger and Brand, *J. Amer. Chem. Soc.*, 1951, **73**, 3509.
[18] Simmonds, Harris, and Fruton, *J. Biol. Chem.*, 1950, **188**, 259.

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this had m. p. 87°, $[\alpha]_D^{18}$ +5·3° (±0·2°) (*c* 6·6 in acetic acid), neutralisation equivalent 298. Later runs gave similar material without counter-current distribution.

Benzyloxycarbonyl-DL-phenylalanine.—The behaviour of this substance somewhat resembled that of the L-isomer. Various m. p.s between 98° and 162° and high neutralisation equivalents were obtained until counter-current distribution yielded material with m. p. 100·5° after recrystallisation from carbon tetrachloride, equivalent 295.

Benzyloxycarbonyl-L-phenylalanylglycine.—Method (b) with phenol-red gave an oil, which was subjected to 358 transfers with 0·5M-KH_2PO_4/0·5M-K_2HPO_4 using the single-withdrawal method on the 100-tube machine. The first material withdrawn was recovered benzyloxycarbonyl-L-phenylalanine (8·5%) (*K* 4·0). The product was spread out in a broad band. Owing to a mechanical defect, 15% of this was lost, but the total yield was estimated to be 92%. The dipeptide derivative was recrystallised from ethyl acetate and had m. p. 154°, $[\alpha]_D^{18}$ −10·2° (±0·2°) (*c* 4·3 in acetic acid).[19, 1]

Benzyloxycarbonyl-L-phenylalanylglycine Ethyl Ester.—Method (c) yielded 83% of the dipeptide derivative, which was recrystallised from ethyl acetate (2 parts)–light petroleum (b. p. 60—80°) (3 parts) and had m. p. 107·5—108·5°, $[\alpha]_D^{16}$ −19·2° (±0·2°) (*c* 4·1 in EtOH).[20]

L-Phenylalanylglycine.—A solution of benzyloxycarbonyl-L-phenylalanylglycine (4·95 g.) in methanol (68 c.c.) and acetic acid (0·68 c.c.) was stirred with palladous oxide catalyst (0·6 g.) while hydrogen was bubbled through it. After 3 hr. no more carbon dioxide could be detected and the filtered solution was evaporated. The dipeptide, which crystallised during the evaporation, was lyophilised (3·24 g.) and then recrystallised twice from water, methanol, or aqueous acetone. The *dihydrate* had $[\alpha]_D^{20}$ +100·0° (±0·3°) (*c* 2·4 in H_2O) (Found, in material equilibrated with the atmosphere: C, 50·7; H, 7·2; N, 10·7. $C_{11}H_{14}O_3N_2,2H_2O$ requires C, 51·1; H, 7·0; N, 10·8%). Drying over phosphoric oxide at 130°/2 mm. for 8 hr. apparently formed some dioxopiperazine, which sublimed [21] (Found, in the residue: C, 60·9; H, 6·2; N, 13·3. Calc. for $C_{11}H_{14}O_3N_2$: C, 59·5; H, 6·4; N, 12·6%). Mixtures of the dihydrate with water (*ca.* 0·02 c.c.) in the proportions of 2, 4, and 6 g. to 10 g. of water were sealed in 4 mm. glass tubes and kept at 21·0° for 3 days. The refractive indices of the solutions were then 1·3648, 1·3650, and 1·3645 respectively.

A sample prepared by the method of Sheehan, Chapman, and Roth [10] from phthaloyl-L-phenylalanylglycine [m. p. 186—187°, $[\alpha]_D^{20}$ −140° (± 0·2°) (*c* 1·7 in EtOH)] had $[\alpha]_D^{17}$ +85·5° (±0·2°) (*c* 2 in H_2O), but this was raised to 100·4° by two recrystallisations from aqueous acetone.

Hydrobromide of L-Phenylalanylglycine Ethyl Ester.—After hydrogenation of benzyloxycarbonyl-L-phenylalanylglycine ethyl ester as in the foregoing experiment, one equivalent of ethanolic hydrogen bromide was added and the hydrobromide, obtained by evaporation, was recrystallised from ethanol–light petroleum (b. p. 60—80°) in large plates, m. p. 134—135°, $[\alpha]_D^{16}$ +40·4° (±0·2°) (*c* 4·2 in H_2O).[11]

Phthaloyl-DL-phenylalanylglycine.—A solution of phthaloyl-DL-phenylalanyl chloride (12·7 g.) [22] in dioxan (180 c.c.) was added during 30 min. to a mixture of glycine (10·6 g.), magnesium oxide (7·3 g.), and water (400 c.c.), which was stirred at 4°. After having been kept for 20 min. at 20°, the solution was acidified with 3N-sulphuric acid (55 c.c.) and thoroughly extracted with ethyl acetate, from which 9·9 g. (62% from phthaloyl-DL-phenylalanine) of *phthaloyl-DL-phenylalanylglycine*, m. p. 128—133° (Found: C, 64·8; H, 4·7; N, 7·9. $C_{19}H_{16}O_5N_2$ requires C, 64·8; H, 4·6; N, 8·0%), was obtained by concentration. The substance was dimorphic; the other *form* had m. p. 163·5—167° (Found: C, 64·3; H, 4·3; N, 8·3%) after recrystallisation from aqueous ethanol, and its crystals repelled each other violently when ground in a mortar. Crystals were obtained for the first time by a 10-transfer distribution with 0·65M-KH_2PO_4/0·35M-K_2HPO_4. The distribution curve corresponded to the presence of 79% of the dipeptide derivative (*K* 1·17), 19·5% of phthaloyl-DL-phenylalanine (*K* 5·66), and 1·5% of an unidentified material (*K* 0·013), probably phthaloyl-DL-phenylalanylglycine.

DL-Phenylalanylglycine.—A solution of phthaloyl-DL-phenylalanylglycine (3·52 g.), phenylhydrazine (4·92 c.c.), and triethylamine (0·98 c.c.) in ethanol (10 c.c.) was boiled [23] for 2 hr.

[19] Behrens, Doherty, and Bergmann, *J. Biol. Chem.*, 1940, **136**, 63.
[20] Anderson and Young, *J. Amer. Chem. Soc.*, 1952, **74**, 5307.
[21] Cf. Gross and Grodsky, *ibid.*, 1955, **77**, 1678.
[22] Sheehan and Frank, *ibid.*, 1949, **71**, 1856.
[23] Cf. Schumann and Boissonas, *Helv. Chim. Acta*, 1952, **35**, 2235.

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Ethyl methyl ketone (25 c.c.) was added, and the solution was boiled for 15 min. further. Acetic acid (4·27 c.c.) was added to the cooled solution, and the dipeptide (1·59 g., 72%) separated. When it was recrystallised from water, large plates or needles were formed (Found, in each form: N, 12·5. Calc. for $C_{11}H_{14}O_3N_2$: N, 12·6%).

*Toluene-*p*-sulphonylglycyl-*L*-phenylalanine.*—This *compound* was obtained by method (b) in a series of runs, and it recrystallised from ethyl acetate–light petroleum (b. p. 40—60°) in needles, m. p. 160·5°, $[\alpha]_D^{16}$ +50·3° (± 0·8°) (*c* 2·55 in EtOH) (Found: C, 57·5; H, 5·3; N, 7·4. $C_{18}H_{20}O_5N_2S$ requires C, 57·4; H, 5·4; N, 7·4%). It is insoluble in 10% aqueous ethanol and hence the yields could be determined by dissolving the acidic product (2 mmole scale) in ethanol (5 c.c.) and adding this solution dropwise with shaking to water (50 c.c.). After the mixture had been stored for 3 hr. at 0°, the pure product, m. p. 160·5°, was collected. The efficiency of this method was confirmed by a 10-transfer distribution with 0·7M-KH_2PO_4/0·3M-K_2HPO_4 of the product of pH 9; the distribution curve showed the presence of 1·72 mmoles of the dipeptide derivative (*K* 1·65) and 0·23 mmole of toluene-*p*-sulphonylglycine (*K* 0·124). The yields obtained with the various initial pH's of coupling were: 6, 75; 7, 78; 7·5, 81; 8, 82; 8·7, 86; 9, 86; 10, 83%.

*Toluene-*p*-sulphonylglycyl-*DL*-phenylalanine.*—This *product*, m. p. 144—145° (Found: C, 57·4; H, 5·2; N, 7·2%), was also obtained by method (b) in a series of runs, and it was isolated by counter-current distribution. Runs were not done below pH 8 because DL-phenylalanine was too insoluble.

*Toluene-*p*-sulphonylglycyl-*DL*-phenylalanylglycine.*—This *compound* was obtained from DL-phenylalanylglycine by method (b) in a series of runs, and recrystallised from ethanol in needles, m. p. 192° (Found: C, 55·6; H, 5·6; N, 9·7. $C_{20}H_{23}O_6N_3S$ requires C, 55·4; H, 5·4; N, 9·7%). The yields were estimated from the weight of the acidic material, which was crystalline although it was a mixture of product and toluene-*p*-sulphonylglycine. The product of the run (2 mmoles scale) at pH 6 was also subjected to a 10-transfer distribution with 0·81M-KH_2PO_4/0·19M-K_2HPO_4, which showed the presence of 1·77 mmoles of product (*K* 0·97) and 0·15 mmole of toluene-*p*-sulphonylglycine (*K* 0·27). Runs at various pH's gave the following respective yields: 6, 87; 7, 88; 7·5, 90; 8, 91; 8·7, 92; 9, 88; 10, 75%.

*Benzyloxycarbonylglycyl-*L*-phenylalanine.*—The product from method (a) (20 mmoles scale) was distributed for 15 transfers with 0·7M-KH_2PO_4/0·3M-K_2HPO_4 (100 c.c. tubes). The distribution curve corresponded to an 86% yield (*K* 1·49) with 15% recovery of benzyloxycarbonylglycine (*K* 0·29). The dipeptide derivative, recrystallised from chloroform, had m. p. 126°, $[\alpha]_D^{14}$ +41·9° (±0·2°) (*c* 2·5 in EtOH)[1].

*Benzyloxycarbonylglycyl-*L*-phenylalanylglycine.*—The product obtained from benzyloxycarbonylglycyl-L-phenylalanine (2 mmoles) by method (b) with initial pH 7·4, was distributed for 96 transfers with 0·75M-KH_2PO_4/0·25M-K_2HPO_4. The optical rotations of the whole of the material contained by tubes 37—40 and 67—70 (*i.e.*, at the two peaks) were $[\alpha]_D^{15}$ +41·6° (±0·1°) (*c* 1·4 in EtOH) and $[\alpha]_D^{15}$ −12·7° (±0·1°) (*c* 2·0 in EtOH) respectively. A redetermination of the rotation of the pure tripeptide derivative,[1] recrystallised from ethyl acetate and having m. p. 162·5—163°, gave $[\alpha]_D^{21}$ −14·6° (±0·3°) (*c* 1·3 in EtOH). The yields of tripeptide derivative (*K* 0·697) and starting material (*K* 2·46) recovered from tubes 22—54 and 56—84 respectively were 83% and 13%.

*Benzyloxycarbonylglycyl-*L*-phenylalanylglycine Ethyl Ester.*—Method (c) gave 81% and 19% of the benzyloxycarbonylglycyl-L-phenylalanine was recovered. A solution of the ester (0·150 g.) in warm ethanol (7·5 c.c.) was stored at 0° and seeded with the racemic ester. No crystals formed in the first hour. After 3 days the crystals were collected and washed with ethanol (2 × 0·5 c.c.), which left 0·093 g., m. p. 119·5—120°, $[\alpha]_D^{20}$ −12·0° (±0·2°) (*c* 2·0 in EtOH).[11]

*Benzyloxycarbonylglycyl-*L*-alanyl-*L*-phenylalanylglycine and the* DL*-Isomer.*—(*a*) Benzyloxycarbonylglycyl-L-alanine (3 mmoles) and L-phenylalanylglycine (3 mmoles) were coupled by method (b) at initial pH 7·4. The mixed products (0·605 g., 42% previously [12] incorrectly reported as 60%; tubes 33—65) and the starting material (0·510 g., 61%; tubes 0—32) were separated by a 96-transfer distribution (3-tube filling) with 0·9M-KH_2PO_4/0·1M-K_2HPO_4. The tetrapeptide derivatives were then subjected to 95 transfers (3-tube filling) with 0·85M-KH_2PO_4/0·15M-K_2HPO_4; the first 20 tubes were then emptied and refilled with equilibrated solvents before recycling distribution was continued for in all 900 transfers. The contents of the tubes were combined in groups of ten and worked up. The distribution curve has already

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been published (Fig. 1 of ref. 12). The *benzyloxycarbonylglycyl-L-alanyl-L-phenylalanylglycine* from tubes 88—99 and 0—17 recrystallised from methanol in needles, m. p. 175°, $[\alpha]_D^{21}$ −31·7° (±0·3°) (*c* 2·5 in 2-methoxyethanol) (Found: C, 59·3; H, 5·7; N, 11·6. $C_{24}H_{28}O_7N_4$ requires C, 59·5; H, 5·8; N, 11·6%). The DL-*diastereoisomer* from tubes 38—67 recrystallised from ethyl acetate in needles, m. p. 177·5°, $[\alpha]_D^{21}$ +14·9° (±0·4°) (*c* 1·9 in 2-methoxyethanol) (Found: C, 59·8; H, 5·7; N, 11·8%).

(*b*) During a similar preparation by method (a), the pH rose on addition of the magnesium carbonate from 5·3 to 6·5 in 2 min., and to 6·9 in 10 min. The first distribution separated the tetrapeptide derivative (*K* 1·02; 78%) from the starting material (*K* 0·197; 23%), and the second distribution was carried out for 847 transfers (5-tube filling). The distribution curve was very similar in shape and correspondence between the experimental points and the theoretical curve to that obtained for the following preparation. The material from the peak (tubes 0—9; *K* 0·560) had specific rotation −31°, whereas that from the trough (tubes 50—59) had specific rotation −18°(±4°) and consequently contained less than 30% of the DL-diastereoisomer, which therefore made up about 0·3% of the total product.

(*c*) Method (c) (3 mmole scale) gave 71% of amorphous benzyloxycarbonyltetrapeptide ester and 30% of benzyloxycarbonylglycyl-L-alanine. A solution of the former in methanol (10 c.c.) was mixed with N-sodium hydroxide (2·26 c.c.) and kept at 20° for 40 min. N-Sulphuric acid (2·26 c.c.) was added and the solvents were evaporated. The residue was partitioned between 3N-sulphuric acid (60 c.c.) and ethyl acetate (200 c.c.), which was then extracted with sodium hydrogen carbonate solution (5 × 20 c.c.) and water (10 c.c.). Only 0·021 g. of oil remained in the ethyl acetate, and the crystalline acid (0·986 g., 71% overall) was subjected to a 900-transfer distribution (5-tube filling); the results have already been published (Fig. 2 of ref. 12; the tube numbers should read 20, 40, 60, 80, 0, 20 from left to right). The material from the trough (tubes 62—71) had specific rotation −33° (±1°).

Bisbenzyloxycarbonyl-L-cystinylbisglycine Diethyl Ester.—This substance [24] was prepared in 81% yield by method (c) and had m. p. 162° after recrystallisation from ethyl acetate.

Acetyl-S-benzyl-L-cysteinylglycine Ethyl Ester.—This *ester* was prepared from acetyl-*S*-benzyl-L-cysteine [25] in 73% yield by method (c) and had m. p. 119° after recrystallisation from ethyl acetate (Found: C, 57·3; H, 6·5; N, 8·4. $C_{16}H_{22}O_4N_2S$ requires C, 56·8; H, 6·6; N, 8·3%).

Benzoylglycyl-DL-serine Methyl Ester [Mrs. B. F. NESBITT].—This *ester* was prepared from hippuric acid in 70% yield by method (c) and had m. p. 89—90° after recrystallisation from ethanol–light petroleum (b. p. 60—80°) (Found: C, 52·6; H, 6·2; N, 9·5. $C_{13}H_{16}O_5N_2,H_2O$ requires C, 52·3; H, 6·1; N, 9·4%).

Benzyloxycarbonyl-L-alanyl-L-tyrosine [Dr. R. J. STEDMAN].—Benzyloxycarbonyl-L-alanine (3 mmoles) and L-tyrosine ethyl ester (3 mmoles) were coupled by method (c); the neutral and the acidic fraction both crystallised in needles and their weights corresponded to a yield of 87% and a recovery of 16%. The ester was dissolved directly in N-sodium hydroxide (5·5 c.c.) by shaking and the solution was kept at 20° for 30 min. The acidic product was separated from a very small neutral fraction, and then crystallised from ethyl acetate–light petroleum (b. p. 40—60°). The overall yield of benzyloxycarbonyldipeptide,[26] m. p. 149—151°, was 66%.

An attempt to couple this substance with glycine ethyl ester by method (c) gave a negligible neutral fraction.

Benzyloxycarbonyl-L-alanyl-O-acetyl-L-tyrosylglycine Ethyl Ester.—Acetic anhydride (0·103 c.c.) was added to a solution of benzyloxycarbonyl-L-alanyl-L-tyrosine (0·338 g.) in N-sodium hydroxide (2·19 c.c.) at 0°. Ice was added and the mixture was left for 15 min. Two drops of aqueous ammonia (*d* 0·88) were added, and after 15 min. further the solution was acidified with dilute hydrochloric acid. The precipitated acetyl derivative (0·352 g.) was collected and recrystallised from ethyl acetate, having m. p. 145·5—146·5° depressed to 140—145° by the starting material.

The acetyl derivative (0·310 g.) was coupled with glycine ethyl ester by method (c), which yielded 62% of neutral powder. The *tripeptide derivative* recrystallised from ethanol as a waxy solid, m. p. 178—178·5° (Found: C, 60·7; H, 6·0; N, 8·5. $C_{26}H_{31}O_8N_3$ requires C, 60·8; H, 6·1; N, 8·2%).

[24] Bergmann and Zervas, *Ber.*, 1932, **65**, 1196.
[25] Du Vigneaud, Wood, and Irish, *J. Biol. Chem.*, 1939, **129**, 173.
[26] Bergmann and Fruton, *ibid.*, 1942, **145**, 251.

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Benzyloxycarbonyl-L-tryptophyl-L-alanine.—The product from method (b) with initial pH 7·4 was distributed for 98 transfers with 0·3M-KH_2PO_4/0·7M-K_2HPO_4; the distribution curve corresponded to the presence of 78% of product (K 2·77) and 22% of starting material (K 8·21). The dipeptide derivative,[27] was recrystallised from chlorobenzene, and had m. p. 155°, $[\alpha]_D^{21}$ −13·2° (±0·3°) (c 4 in EtOH).

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[27] Smith, *J. Biol. Chem.*, 1948, **175**, 45.

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265. *Peptides. Part VII.* The Preparation and Use of* p-*Nitrophenyl Thiolesters.*†

By J. A. FARRINGTON, P. J. HEXTALL, G. W. KENNER, and J. M. TURNER.

Tri-*p*-nitrophenyl phosphorotrithioite (II) converts the benzyloxycarbonyl derivatives of peptides or amino-acids into the corresponding *p*-nitrophenyl thiolesters (I). These thiolesters react with aqueous solutions of peptides or amino-acids at room temperature. Both stages of this peptide synthesis proceed in good yield, but racemisation is liable to occur during the second.

WIELAND and his co-workers [1,2] have shown that peptide links can be formed in aqueous media from phenyl thiolesters, because they are stable to hydrolysis and yet react with amines, albeit rather slowly. Our experiences, described later in this paper, with *p*-nitrophenyl esters suggested that the *p*-nitrophenyl thiolesters (I) would react faster ‡ and might be even more valuable than Wieland's intermediates.

Benzyloxycarbonylglycine *p*-nitrophenyl thiolester was prepared, like the phenyl analogue,[1] from the mixed anhydride with ethyl hydrogen carbonate.[3] Its solution in dioxan reacted smoothly at 18° with aqueous solutions of phenylalanine and phenylalanylglycine, the red colour of the liberated *p*-nitrothiophenoxide anion providing a convenient indication of the reaction. The best way of buffering the reaction mixture was to stir it with magnesium carbonate.

Completely racemic *p*-nitrophenyl thiolester was obtained from benzyloxycarbonylglycyl-L-phenylalanine through the carbonic mixed anhydride. The mixed anhydride with lithium hydrogen sulphate [4,5] gave a moderate yield of optically active thiolester. That this specimen was partly racemic was suggested by the products of reaction with glycine and glycine ester, and this was confirmed later when genuine L-material became available. Both the sulphuric anhydride mentioned above and that derived from benzyloxycarbonylglycine consumed the full molar proportion of *p*-nitrothiophenol, and some of

* Part VI, preceding paper.

† A preliminary account has appeared (Farrington, Kenner, and Turner, *Chem. and Ind.*, 1955, 601).

‡ *p*-Nitrothiophenol has pK 6·8 in 1 : 2 (v/v) dimethylformamide–0·2M-potassium phosphate (determined from absorption at 448 mμ). In water the pK was estimated as 4·5; accurate determination was frustrated by the insolubility of *p*-nitrothiophenol.

[1] Wieland, Schäfer, and Bokelmann, *Annalen*, 1951, **573**, 99.
[2] Wieland and Schäfer, *ibid.*, 1952, **576**, 104.
[3] Boissonas, *Helv. Chim. Acta*, 1951, **34**, 874; Vaughan and Osato, *J. Amer. Chem. Soc.*, 1952, **74**, 676.
[4] Kenner and Stedman, *J.*, 1952, 2069.
[5] Clayton, Farrington, Kenner, and Turner, preceding paper.

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this was regenerated when the aqueous liquors were boiled. Very likely lithium *S*-*p*-nitrophenyl thiosulphate is a by-product of attack on the sulphur, instead of the carbon, in the mixed anhydride.

$R{\cdot}CO{\cdot}S{\cdot}C_6H_4{\cdot}NO_2$ (I) $P(S{\cdot}C_6H_4{\cdot}NO_2)_3$ (II) $C_6H_5{\cdot}NH{\cdot}C(:N{\cdot}C_6H_5){\cdot}S{\cdot}C_6H_4{\cdot}NO_2$ (III)

A new method for converting carboxylic acids into thiolesters was clearly needed and we explored the use of tervalent phosphorus derivatives of *p*-nitrothiophenol, following the preparation of anilides from *N*-arylphosphenimidous anilides.[6] Finally a good reagent was discovered, namely, tri-*p*-nitrophenyl phosphorotrithioite (II). It is a stable crystalline solid, prepared from phosphorus trichloride and a salt of *p*-nitrothiophenol; our preferred method avoids the somewhat troublesome preparation of sodium *p*-nitrothiophenoxide by starting from *S*-*p*-nitrophenyl-*NN'*-diphenyl*iso*thiourea (III), which is readily available from *p*-nitrobenzenediazonium chloride and thiocarbanilide.[7] Excellent yields of *p*-nitrophenyl thiolesters were obtained with the reagent (II) by three methods. The carboxylic acid was allowed to react directly in warm dimethylformamide or in pyridine, or a solution of its lithium salt in dimethylformamide was shaken with the reagent at room temperature. In each instance the reaction mixture was anhydrous and the neutral product isolated after being washed with sodium hydrogen carbonate solution. The lithium salts reacted faster than the free acids, but the first method gave the most consistent yields of easily purified material. Presumably the other reaction product was either the *SS'*-di-*p*-nitrophenyl ester of phosphorodithious (or phosphonodithoic) acid or its lithium salt as the case might be, but we were unable to isolate it. It was evidently destroyed during the working-up, for the red colour of *p*-nitrothiophenoxide anion developed in the bicarbonate washings. Normally the reagent (II) and the carboxylic acid were mixed in equimolar proportions, but when 3 mol. of benzyloxycarbonylglycine lithium salt were added 2 mol. of thiolester were obtained.

The benzyloxycarbonylglycyl-L-phenylalanine *p*-nitrophenyl thiolester obtained from the phosphorotrithioite (II) had double the optical rotation of that prepared from the sulphuric anhydride. Furthermore it gave benzyloxycarbonylglycyl-L-phenylalanylglycine of good quality in high yield when it was allowed to react with glycine in aqueous dioxan. But it had already been found in a study of the sulphuric anhydride synthesis [5] that racemisation is more likely to occur during the condensation of benzyloxycarbonylglycyl-L-alanine with L-phenylalanylglycine. The benzyloxycarbonyltetrapeptide was therefore prepared by the thiolester method and analysed by counter-current distribution.[5] This revealed the presence of almost half as much DL- as LL-isomer, a much worse result than that of the sulphuric anhydride method. Unrestricted application of the new method cannot therefore be advocated, but the relatively great tendency to crystallisation and stability of the *p*-nitrophenyl thiolesters and the unusually high yields will render it valuable in certain instances. These will be chiefly syntheses through the thiolesters of either benzyloxycarbonylamino-acids or derivatives of peptides with *C*-terminal glycine, neither of which are prone to racemisation; some examples are described in the Experimental section. A special application is to the synthesis of cyclic peptides.[8]

Before working with *p*-nitrophenyl thiolesters we investigated the use of analogous oxygen compounds. These are, in principle, more directly accessible from carboxylic acids, like the cyanomethyl esters which have been so successfully used for peptide synthesis.[9] However, despite the fact that small amounts of dinitrophenylpeptides may be produced during the dinitrophenylation of amino-acids,[10] we were unable to effect reaction of benzyloxycarbonylglycine lithium salt with either fluorodinitrobenzene or

[6] Grimmel, Guenther, and Morgan, *J. Amer. Chem. Soc.*, 1946, **68**, 539.
[7] Busch and Schulz, *J. prakt. Chem.*, 1938, **150**, 180.
[8] Kenner and Turner, *Chem. and Ind.*, 1955, 602.
[9] Schwyzer and co-workers, *Helv. Chim. Acta*, 1955, **38**, 80, 83, 1508.
[10] Heikens, Hermans, and van Velden, *Nature*, 1954, **174**, 1187.

picryl chloride. Benzyloxycarbonylglycine *p*-nitrophenyl ester was prepared in moderate yield from *p*-nitrophenol and the mixed anhydrides with both ethyl and lithium hydrogen sulphate; in the latter instance reaction was notably easier in aqueous than in anhydrous dimethylformamide. The reactivity of this *p*-nitrophenyl ester towards alanine was greater than that of the corresponding phenyl thiolester but less than that of the *p*-nitrophenyl thiolester (ratio of rates, 16 : 1 : 140). The *p*-nitrophenyl ester obtained from benzyloxycarbonylglycyl-L-phenylalanine through the sulphuric anhydride had a small optical rotation but it gave the DL-tripeptide derivative on reaction with glycine. Consequently our work along these lines [11] was abandoned. Very recently a *p*-nitrophenyl ester has been prepared by a new route and applied to the synthesis of gramicidin-S.[12]

Experimental

M. p.s are corrected. Evaporations were carried out under reduced pressure.

Tri-p-nitrophenyl Phosphorotrithioite.—(*a*) A solution of lithium hydroxide (2·21 g.; commercial dihydrate) in water (25 c.c.) was added to a solution of *S-p*-nitrophenyl-*NN'*-diphenyl*iso*-thiourea [7] (17·5 g.; m. p. 133°) in dimethylformamide (75 c.c.), which was immediately coloured deep red. The water was removed, under 15 mm. of nitrogen, through a 6 in. column of steel gauze rings in 50 c.c. of distillate. The solution was cooled to 0° and stirred under nitrogen while phosphorus trichloride (1·46 c.c.; freshly distilled from diethylaniline) was added dropwise. As the addition was completed the mixture changed from red to yellow. It was stirred for 15 min. further at 0°, and the *trithioite* (5·7 g., 70%) was then collected, washed with dimethyl formamide (6 c.c.), and dried at 80°/3 mm. before being recrystallised from ethylene dichloride in yellow needles, m. p. 166—167° (Found: C, 43·8; H, 2·6; N, 8·8. $C_{18}H_{12}O_6N_3S_3P$ requires C, 43·8; H, 2·5; N, 8·5%). It may be dimorphic since analytically pure products of different preparations had m. p.s as much as 18° lower.

(*b*) A solution of partly hydrated sodium *p*-nitrothiophenoxide (60 g.) in pyridine (600 c.c.) was dried by concentration to 500 c.c. under a Fenske fractionating column. After a small amount of brown material had been removed at a centrifuge, the solution was stirred and cooled in ice. Phosphorus trichloride diluted with 10 vols. of pyridine was added slowly until the intense red colour suddenly faded to orange-pink. The colloidal salt was separated centrifugally and the liquors were set aside for a week at −40°. The trithioite which crystallised (35 g.) was collected and a further crop (10 g.) was obtained by evaporation of the liquor. Recrystallisation from chlorobenzene afforded 27 g., of m. p. 155°.

General Procedures for Preparation of p-Nitrophenyl Thiolesters from Tri-p-nitrophenyl Phosphorotrithioite.—(a) *In dimethylformamide.* Tri-*p*-nitrophenyl phosphorotrithioite (20 mmoles; dried at 40°/0·5 mm. for 8 hr.) was added to a solution, which had been dried by concentration at 50°/11 mm., under a 6 in. column packed with steel gauze, of the carboxylic acid (20 mmoles) in dimethylformamide (40 c.c.). The mixture was stirred under nitrogen at 85° for 20 min., during which the trithioite dissolved. The solution was evaporated and the residue, apart from some di-*p*-nitrophenyl disulphide, was taken up in ethyl acetate (200 c.c.) and water (50 c.c.). The ethyl acetate solution was washed with saturated sodium hydrogen carbonate solution (3 × 50 c.c.) and water (3 × 50 c.c.) before being evaporated. The almost colourless residue was taken up again in ethyl acetate (15 c.c.), which was then filtered from a little bisnitrophenyl disulphide and evaporated, yielding the product. The small amount of unchanged acid could be recovered from the alkaline washings, after they had been treated with a few drops of 30% hydrogen peroxide, filtered, and washed with ethyl acetate, by acidification and extraction with ethyl acetate.

(b) *In pyridine.* Tri-*p*-nitrophenyl phosphorotrithioite (10 mmoles) was added to a solution of the carboxylic acid (9·5 mmoles) in dry pyridine (15 c.c.). The mixture was kept at 60° for 5 min. so that all had dissolved, and then left overnight at 18°. The residue from evaporation of the pyridine was taken up in ethyl acetate (100 c.c.), which was washed successively with 50 c.c. portions of N-sulphuric acid, water, saturated sodium hydrogen carbonate solution

[11] Cf. Bodánszky, *Nature*, 1955, **175**, 685; Bodánszky, Szelke, Tömörkeny, and Weisz, *Chem. and Ind.*, 1955, 1517; Wieland and Jaenicke, *Annalen*, 1956, **599**, 125.
[12] Schwyzer and Sieber, *Angew. Chem.*, 1956, **68**, 518.

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(twice), and water. The ethyl acetate was combined with back-extracts of the aqueous washings and evaporated to yield the product. Any unchanged acid could be recovered from alkaline washings as in (a).

(c) *Through the lithium salt.* A solution of the carboxylic acid (5 mmoles) in dimethylformamide (65 c.c.) was neutralised with methanolic lithium methoxide and then dried by concentration at 50°/11 mm., under a 6 in. column of steel gauze rings. The solution (50 c.c.) was cooled to 20° and treated with tri-*p*-nitrophenyl phosphorotrithioite (5 mmoles), which dissolved on shaking. The solution was kept overnight and then either poured into water or evaporated and worked up as in (b).

Benzyloxycarbonylglycine p-*Nitrophenyl Thiolester.*—(a) *From tri*-p-*nitrophenyl phosphorotrithioite.* Procedure (a) described above gave 96%, procedure (b) gave 99%, and procedure (c) gave 96% of the *thiolester*, which recrystallised from methanol, benzene, or aqueous acetone in colourless needles, m. p. 112·5° (Found : C, 55·7; H, 4·2; N, 8·3. $C_{16}H_{14}O_5N_2S$ requires C, 55·5; H, 4·1; N, 8·1%).

(b) *From the carbonic anhydride.* Ethyl chloroformate (0·48 c.c., 5 mmoles) was added dropwise to a stirred solution of benzyloxycarbonylglycine (1·045 g., 5 mmoles) and triethylamine (0·675 c.c., 5 mmoles) in dimethylformamide (50 c.c.) at −5°. After 10 min. a solution of sodium *p*-nitrothiophenoxide (0·885 g., 5 mmoles) in dimethylformamide (15 c.c.) was added, and the mixture was left overnight at 18°. Working according to the phosphorotrithioite procedure (b) then furnished 65% of orange crystalline thiolester.

(c) *From the sulphuric anhydride.* Sodium *p*-nitrothiophenoxide (1·77 g., 10 mmoles) was dissolved in a mixture 0·5M-potassium dihydrogen phosphate (93 c.c.), 0·5M-dipotassium hydrogen phosphate (40 c.c.), and dimethylformamide (67 c.c.). The solution was added to a solution of lithium benzyloxycarbonylglycyl sulphate [5] (10 mmoles) in dimethylformamide (100 c.c.), and the mixture was stirred at 18° during 15 hr. while the thiolester precipitated. The red colour faded to about half its intensity in ½ hr. and was regularly pale orange after 1½ hr. The pH was brought to 4 with 3N-sulphuric acid, and the solvents were evaporated before working-up as before; the yield was 70%. When the reaction was carried out in anhydrous dimethylformamide the yield was 30% after 4 hr., 50% after 19 hr., 67% after 66 hr.

*Benzyloxycarbonylglycyl-*L*-phenylalanine* p-*Nitrophenyl Thiolester.*—(a) *From tri*-p-*nitrophenyl phosphorotrithioite.* Procedure (c), followed by recrystallisation from methanol, afforded 79% of the *thiolester* as colourless needles, m. p. 154—155°, $[\alpha]_D^{16}$ −67·0° (±0·4°) (*c* 4·6 in dioxan) (Found : C, 61·0; H, 4·5; N, 8·6. $C_{25}H_{23}O_6N_3S$ requires C, 60·9; H, 4·7; N, 8·5%).

(b) *From the carbonic anhydride.* The preparation followed the plan of the glycine series except that *p*-nitrothiophenol itself was added instead of the sodium salt, and it afforded 81% of thiolester, which had, after recrystallisation, m. p. 154—155°, $[\alpha]_D^{17}$ +0·6° (*c* 3·7 in dioxan).

(c) *From the sulphuric anhydride.* The preparation followed the plan of the glycine series except that the precipitated thiolester (53%) was collected directly. After recrystallisation it had m. p. 152—153°, $[\alpha]_D^{17}$ −35·7° (*c* 3·2 in dioxan).

*Benzyloxycarbonyl-*L*-leucine* p-*Nitrophenyl Thiolester.*—Procedure (a) afforded 97% of the *thiolester*, which recrystallised from methanol in colourless needles, m. p. 107° (Found : C, 59·9; H, 5·2; N, 6·8. $C_{20}H_{22}O_5N_2S$ requires C, 59·7; H, 5·5; N, 7·0%).

*Benzyloxycarbonyl-*L*-leucylglycine* p-*Nitrophenyl Thiolester.*—Procedure (a) afforded 96% of the *thiolester*, which recrystallised from methanol or benzene–light petroleum (b. p. 40—60°) in colourless needles, m. p. 118° (Found : C, 57·7; H, 5·2; N, 9·5. $C_{22}H_{25}O_6N_3S$ requires C, 57·5; H, 5·5; N, 9·2%).

*Benzyloxycarbonylglycyl-*L*-leucylglycine* p-*Nitrophenyl Thiolester.*—Procedures (a) and (b) both gave 98% of the *thiolester*, which had, after recrystallisation from aqueous acetone, m. p. 159° (Found : C, 55·6; H, 5·2; N, 10·8. $C_{24}H_{28}O_7N_4S$ requires C, 55·8; H, 5·5; N, 10·8%).

*Benzyloxycarbonylglycyl-*L*-leucylglycyl-*L*-leucylglycine* p-*Nitrophenyl Thiolester.*—Procedure (a) gave 93%, while procedure (b) gave 98%, of the *thiolester*, which had, after recrystallisation from aqueous acetone, m. p. 184° (Found : C, 55·9; H, 6·1; N, 12·3. $C_{32}H_{42}O_9N_6S$ requires C, 56·0; H, 6·2; N, 12·2%).

L-2-p-*Nitrophenylthiocarbonyl-5-oxo-1-toluene-*p-*sulphonylpyrrolidine.*—This *thiolester* was prepared in quantitative yield from 5-oxo-1-toluene-*p*-sulphonylpyrrolidine-2-carboxylic acid [13] by procedure (b). It was recrystallised from aqueous acetone and had m. p. 174° (Found : C, 51·0; H, 4·0; N, 6·7. $C_{18}H_{16}O_6N_2S_2$ requires C, 51·4; H, 3·8; N, 6·7%).

[13] Rudinger, *Coll. Czech. Chem. Comm.*, 1954, **19**, 375.

Benzyloxycarbonyl-L-leucylglycine.—A solution of benzyloxycarbonyl-L-leucine *p*-nitrophenyl thiolester (8·0 g.) in tetrahydrofuran (80 c.c.) and one of glycine (3·0 g.) in water (60 c.c.) were shaken together with magnesium carbonate (8 g.) at 18° during 40 hr. The solvents were evaporated and the residue was partitioned between ethyl acetate (200 c.c.) and N-sulphuric acid (60 c.c.). The ethyl acetate was extracted with sodium hydrogen carbonate solution (2 × 100 c.c.); the extract was rendered colourless by a little hydrogen peroxide before being filtered and washed with ethyl acetate. The product (6·3 g., 98%) was recovered from the sodium hydrogen carbonate solution by acidification, extraction with ethyl acetate, and evaporation. It recrystallised from ethyl acetate–light petroleum (b. p. 40—60°) in colourless prisms, m. p. 117—118°.[14]

L-*Leucylglycine Hydrobromide.*—Benzyloxycarbonyl-L-leucylglycine (1·61 g.), in acetic acid (20·5 c.c.), was treated with 6N-hydrogen bromide in acetic acid (4·5 c.c.). The mixture was kept for 2 hr. at 18°. The residue obtained by evaporation was triturated with ether, which left colourless crystals (1·34 g.). These were used directly for further preparations, but the pure *hydrobromide* was obtained by recrystallisation from ethereal methanol in colourless prisms, m. p. 194—195° (Found: C, 35·8; H, 6·7; N, 10·2. $C_8H_{17}O_3N_2Br$ requires C, 35·7; H, 6·4; N, 10·4%).

Benzyloxycarbonylglycyl-L-leucylglycine.—(*a*) The corresponding ethyl ester [5] (9·58 g.) was shaken overnight with 0·5N-sodium hydroxide (50 c.c.). The solution was washed with ethyl acetate and then acidified with N-sulphuric acid. The precipitated oil was extracted into ethyl acetate (100 c.c.) before being purified by counter-current distribution (14 transfers; 100 c.c. phases) between ethyl acetate and 0·82M-KH_2PO_4–0·18M-K_2HPO_4. Tubes 1—7 contained 8·6 g. of highly crystalline material (*K* 0·25), recrystallisation of which from ethyl acetate furnished pure *benzyloxycarbonylglycyl-L-leucylglycine* (7·99 g., 89%), m. p. 110°, $[\alpha]_D^{19}$ −14·7° (*c* 4 in dimethylformamide) (Found: C, 57·2; H, 6·3; N, 11·1. $C_{18}H_{25}O_6N_3$ requires C, 57·0; H, 6·6; N, 11·1%).

(*b*) Magnesium carbonate (3 g.) and solutions of benzyloxycarbonylglycine *p*-nitrophenyl thiolester (1·73 g.) in tetrahydrofuran (40 c.c.) and L-leucylglycine hydrobromide (1·345 g.) in water (40 c.c.) were used in a preparation like that of benzyloxycarbonyl-L-leucylglycine. The yield of material, m. p. 104—105°, was 1·77 g. (93%).

Benzyloxycarbonylglycyl-L-leucylglycyl-L-leucylglycine.—A preparation, like the foregoing preparation (b), from benzyloxycarbonylglycyl-L-leucylglycine *p*-nitrophenyl thiolester (1·32 g.) and L-leucylglycine hydrobromide (0·72 g.) gave an amorphous product (1·31 g., 93%), m. p. 205—206°, which was characterised as its crystalline *p*-nitrophenyl thiolester (see above). On counter-current distribution (14 transfers; 100 c.c. phases) between ethyl acetate and 0·20M-KH_2PO_4–0·05M-K_2HPO_4 it appeared homogeneous (*K* 0·12), but it would not have been separated from benzyloxycarbonylglycyl-L-leucylglycine (*K* 0·15).

Benzyloxycarbonylglycyl-L-phenylalanine.—A solution of L-phenylalanine (3·14 g., 19 mmoles) in water (190 c.c.) was added to a solution of benzyloxycarbonylglycine *p*-nitrophenyl thiolester (6·58 g., 19 mmoles) in dioxan (285 c.c.). The clear yellow solution had pH 5·8 (to indicator paper) and this was raised to and maintained at 7·5 by gradual addition during 1 hr. of N-sodium hydroxide (38 c.c.). The mixture was left overnight at 18° and it was then treated in the usual way. The product (6·31 g., 93%) had m. p. 124—125°.[15]

Benzyloxycarbonylglycyl-DL-phenylalanylglycine.—DL-Phenylalanylglycine (0·111 g., 0·5 mmole) was dissolved in 0·5M-potassium dihydrogen phosphate (3 c.c.) and 0·5M-dipotassium hydrogen phosphate (7 c.c.) and then stirred at 18° during 16 hr. with a solution of benzyloxycarbonylglycine *p*-nitrophenyl thiolester (0·173 g., 0·5 mmole) in dioxan (20 c.c.). The product (0·185 g., 90%), obtained in the usual way, had m. p. 140·5—142°.[16]

Benzyloxycarbonylglycyl-L-phenylalanylglycine.—(*a*) A preparation, similar to those described above, from benzyloxycarbonylglycyl-L-phenylalanine *p*-nitrophenyl thiolester, glycine, and magnesium carbonate in aqueous dioxan, furnished a quantitative yield of the tripeptide derivative,[16, 5] m. p. 156—157°, $[\alpha]_D^{18}$ −14·6° (±0·3°) (*c* 3·8 in EtOH).

(*b*) A mixture of glycine ethyl ester hydrochloride (0·070 g., 0·25 mmole), triethylamine (0·068 c.c., 0·5 mmole), and dimethylformamide (4 c.c.) was added dropwise to a solution of the same thiolester (0·123 g., 0·25 mmole) in dimethylformamide (2 c.c.). The solution, which

[14] Bergmann, Zervas, and Fruton, *J. Biol. Chem.*, 1935, **111**, 238.
[15] Hofmann and Bergmann, *ibid.*, 1940, **134**, 225.
[16] Kenner and Stedman, *J.*, 1952, 2074.

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immediately became red, was left for 16 hr. at 18° and then evaporated to dryness. The neutral product was isolated by the usual separations between ethyl acetate and 3N-sulphuric acid, saturated sodium hydrogen carbonate solution, and water. Hydrolysis of it at 18° by a slight excess of dilute sodium hydroxide in 80% methanol gave 0·099 g. (96%) of material with m. p. 156—157°, $[\alpha]_D^{18}$ −13·7° (±0·3°) (*c* 3·4 in EtOH).

*Benzyloxycarbonylglycyl-*L*-alanyl-*L*-phenylalanylglycine and the* DL*-Isomer.*—Benzyloxycarbonylglycyl-L-alanine (0·560 g., 2 mmoles) was converted by procedure (c) into the thiolester, which was isolated by extraction with ethyl acetate as an orange, partly crystalline material (1·21 g.); 9% of the starting material was recovered unchanged. The crude thiolester was dissolved in dioxan (20 c.c.) and then stirred with magnesium carbonate and a solution of L-phenylalanylglycine (0·480 g. of the hydrate, 2 mmoles) in water (10 c.c.) during 12 hr. at 20°. The solvents were evaporated in a current of air and the residue was partitioned between 3N-sulphuric acid (20 c.c.) and ethyl acetate (60 c.c.), which was then extracted with saturated sodium hydrogen carbonate solution (5 × 10 c.c.; first portion containing 0·7 c.c. 20-vol. hydrogen peroxide). The carbonate solution was filtered, acidified with concentrated hydrochloric acid, and extracted with ethyl acetate (100 c.c., 2 × 50 c.c.). Evaporation of the ethyl acetate yielded crystals (0·922 g.) which were handled as before.[5] The first distribution (94 transfers, 5-tube filling) separated the tetrapeptide derivatives (0·763 g., 79%; tubes 34—65) from benzyloxycarbonylglycyl-L-alanine (0·037 g., 5%; tubes 0—33) and bis-*p*-nitrophenyl-disulphide (0·141 g., tubes 66—94). The second distribution (850 transfers, 5-tube filling) of the tetrapeptide derivatives showed that 70% was the LL- (*K* 0·582) and 30% was the DL-form (*K* 0·742). In agreement with previous findings [5] the optical rotations were −31·5° and +14·9° respectively.

Benzyloxycarbonylglycine p-*Nitrophenyl Ester.*—(*a*) Ethyl chloroformate (0·96 c.c., 10 mmoles) was added dropwise to a stirred solution of benzyloxycarbonylglycine (2·09 g., 10 mmoles) and triethylamine (1·35 c.c. 10 mmoles) in dry toluene (50 c.c.) at 0°, and the mixture was stirred at 0° for 10 min. further. A solution of *p*-nitrophenol (1·39 g., 10 mmoles) in toluene (20 c.c.) and dimethylformamide (10 c.c.) was added. The mixture was left for 15 hr. at 20° and then heated for 1 hr. at 50°. The toluene solution was washed with 0·1N-hydrochloric acid (2 × 50 c.c.), saturated sodium hydrogen carbonate solution (4 × 50 c.c.), and water (2 × 10 c.c.) before being evaporated. The p-*nitrophenyl ester* (1·53 g., 46%) recrystallised from methanol in colourless needles, m. p. 128° (Found: C, 58·1; H, 4·0; N, 8·7. $C_{16}H_{14}O_6N_2$ requires C, 58·2; H, 4·3; N, 8·5%).

(*b*) A solution of *p*-nitrophenol (1·39 g., 10 mmoles) in 0·5N-sodium hydroxide (20 c.c.) was added to a solution of lithium benzyloxycarbonylglycyl sulphate [5] (10 mmoles) in dimethylformamide (28 c.c.). A precipitate was formed rapidly, but the mixture was left overnight at 18° before being worked up in the usual way. *p*-Nitrophenol was removed from the neutral product (2·03 g., 60%) by sublimation; 40% of the benzyloxycarbonylglycine was recovered. A preparation from lithium *p*-nitrophenoxide in anhydrous dimethylformamide, which was allowed 4 days at 50° for reaction, gave only a 28% yield; lithium sulphate, which is sparingly soluble in dimethylformamide, did not separate from the reaction mixture.

Relative Reactivities of Derivatives of Benzyloxycarbonylglycine.—0·1M-L-Alanine (5 c.c.) was added to a solution of the *p*-nitrophenyl ester, phenyl thiolester, or *p*-nitrophenyl thiolester of benzyloxycarbonylglycine (0·5 mmole) in dioxan (10 c.c.) at 21°. The pH of the clear solution was measured by means of a glass electrode and it was maintained at a predetermined value (7·5, 8, 8·5, 9, or 9·5) by addition of N-sodium hydroxide from a micrometer syringe. The pK_a of alanine being taken as 10·0, the amount of sodium hydroxide used in overcoming the buffering effect of the alanine and the concentration of the alanine anion could be calculated. The relative specific rates of reaction between the anion and the several esters could then be derived from the volumes of alkali consumed in given times: they were in the ratio 16 : 1 : 140.

Other Reactions of Benzyloxycarbonylglycine p-*Nitrophenyl Ester.*—(*a*) Benzyloxycarbonylglycylglycine (90%) was obtained from reaction between the ester and glycine in ethanol and potassium phosphate buffer.

(*b*) Benzyloxycarbonylglycylglycine ethyl ester (94%) was obtained from reaction between the ester, glycine ethyl ester, and triethylamine in ethanol.

(*c*) Benzyloxycarbonylglycyl-L-phenylalanine (32%) was obtained from reaction between the ester and L-phenylalanine in dioxan and potassium phosphate buffer. Probably insufficient time had been allowed for reaction.

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Benzyloxycarbonylglycylphenylalanine p-*Nitrophenyl Ester.*—A solution of *p*-nitrophenol (0·695 g., 5 mmoles) in N-sodium hydroxide (5 c.c.), 0·5M-potassium dihydrogen phosphate (70 c.c.), and 0·5M-dipotassium hydrogen phosphate (30 c.c.) was added to a solution of lithium benzyloxycarbonylglycyl-L-phenylalanyl sulphate [5] (5 mmoles) in dimethylformamide (50 c.c.) at 0°. The mixture was left overnight at 18° and the precipitated p-*nitrophenyl ester* (0·890 g., 37%) was collected and recrystallised from methanol in colourless crystals, m. p. 133°, $[\alpha]_D^{17}$ +2·0° (±0·3°) (*c* 2·6 in dioxan) (Found: C, 63·2; H, 4·7; N, 8·8. $C_{25}H_{23}O_7N_3$ requires C, 62·9; H, 4·9; N, 8·8%). It cannot be concluded from the optical rotation alone that the material is almost completely racemic because the rotations of the free acid and the *p*-nitrophenyl thiolester are +41·5° (in EtOH) and −67·0° (in dioxan) respectively. However, reaction between the *p*-nitrophenyl ester and glycine in aqueous dioxan buffered with magnesium carbonate gave benzyloxycarbonylglycyl-DL-phenylalanylglycine.

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266. *The Infrared Spectra of Some Diacylamines in the 6 μ Region.*

By R. A. ABRAMOVITCH.

Diacetylamino-compounds show more than one amide carbonyl stretching band in the 6 μ region, but in dilute solution and with a slit schedule of 1·5 mm. only one band is observed; this is resolvable into its component bands at narrower slit schedules. Dilution experiments show the absence of molecular association. The multiplicity of bands is attributed to vibrational coupling of the C=O groups.

DURING a study of the 1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carbolines it was observed [1] that a 2-acetyl derivative exhibited two bands, attributed to amide carbonyl stretching vibrations, in the 6 μ infrared region. Similar observations had been made [2] on compounds containing the group −CO−NH−CO− in a cyclic structure, *e.g.*, succinimides; the two bands found, one between 5·6 μ and 5·8 μ and the other between 5·85 μ and 6·00 μ, were assigned one to each of the cyclic carbonyl groups. Spectra of solutions and solid were reported to be very similar and the absence of hydrogen bonding was demonstrated by the fact that *N*-pentylsuccinimide also had both bands. On the other hand, *N*-bromosuccinimide has only one band [3] at 1732 cm.$^{-1}$ in solution (1710 cm.$^{-1}$ in the solid state). Molecules containing the group −CO−NR−CO− not as part of a ring have not been investigated systematically. In some cases one band is reported for diacylamino-compounds, in others two. Grove, Jeffs, and Rustidge [4] and Witkop and Patrick [5] have reported the spectra of a number of substituted *NN*-diacetylanilines, as summarised in Table 1. Their data seem to indicate that if the diacetylamine is symmetrically substituted only one carbonyl band is observed in the 6 μ region, whereas if it is unsymmetrically substituted, two bands are observed. This is not in accord with the results obtained with the succinimides, for instance, where symmetrical ring compounds show two carbonyl bands.[2] A single band at 1694 cm.$^{-1}$ is reported by Orr, Sims, and Manson [6] for an unsymmetrically

[1] Abramovitch, *J.*, 1956, 4593.
[2] Randall, Fowler, Fuson, and Dangl, "Infrared Determination of Organic Structures," Van Nostrand, New York, 1949, p. 14.
[3] Gierer, *Z. Naturforsch.*, 1953, **8b**, 654.
[4] Grove, Jeffs, and Rustidge, *J.*, 1956, 1956.
[5] Witkop and Patrick, *J. Amer. Chem. Soc.*, 1952, **74**, 3861.
[6] Orr, Sims, and Manson, *J.*, 1956, 1337.

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substituted dibenzoylamino-compound, whereas diacetylamine itself is stated to exhibit a single carbonyl peak at 1708 cm.$^{-1}$ (in chloroform). Simple *NN*-diacetylanilines have now been examined to see whether there is any justification in the apparent pattern: symmetrical, one band; unsymmetrical, two bands. The compounds studied include

TABLE 1.

Compound	Ref.	ν (cm.$^{-1}$)
2 : 6-Diacetoxy-*NN*-diacetyl-4-methoxyaniline	4	1717 [a]
NN-Diacetyl-2 : 6-dibenzyloxy-4-methoxyaniline	4	1710 [a]
2 : 4-Diacetoxy-*NN*-diacetyl-6-methoxyaniline	4	1730, 1705 [a]
NN-Diacetyl-2-benzyloxy-4 : 6-dimethoxyaniline	4	1716, 1696 [a]
2-Acetoxy-*NN*-diacetyl-4 : 6-dimethoxyaniline	4	1719, 1706 [a]
4-Acetoxy-*NN*-diacetyl-2 : 6-dimethoxyaniline	4	1715 [a]
NN-Diacetyl-2-benzoyloxyaniline	5	1724, 1712 [b]
2-Acetoxy-*NN*-diacetylaniline	5	1730, 1709 [b]
NN-Diacetyl-2-methoxyaniline	5	1718, 1706 [b]

[a] Nujol mull. [b] Chloroform solution.

symmetrically and unsymmetrically monosubstituted diacetylanilines, diacetylbenzylamine, and diacetylnaphthylamines. A number of mixed diacylamines (acyl groups not identical) were also examined, and succinimide and *N*-bromosuccinimide re-examined.

EXPERIMENTAL

Most of the diacetylanilines were prepared by Sudborough's general method.[7] *NN*-Diacetyl-*o*-anisidine was prepared as described by Witkop and Patrick,[5] and *NN*-diacetylbenzylamine as described by Holmes and Ingold.[8]

NN-*Diacetyl*-m-*toluidine* had b. p. 164—168°/16 mm. (Found: C, 68·8; H, 7·1. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8%).

NN-*Diacetyl*-p-*anisidine* formed needles, m. p. 60° [from light petroleum (b. p. 40—60°)] (Found: C, 63·5; H, 6·5. $C_{11}H_{13}O_3N$ requires C, 63·8; H, 6·3%).

N-Acetyloxindole was prepared as described by Suida.[9] 2-Acetyl-1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline has already been described.[1]

2-*Acetyl*-1 : 2 : 3 : 4-*tetrahydro*-9-*methyl*-1-*oxo*-β-*carboline*.—1 : 2 : 3 : 4-Tetrahydro-9-methyl-1-oxo-β-carboline [1] was refluxed for 2 hr. with an excess of acetic anhydride and a few drops of acetic acid, and the solution poured into water. The *product* crystallised from methanol in colourless rods, m. p. 108—109° (Found: C, 69·4; H, 7·2. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 7·3%).

TABLE 2. *Amide carbonyl frequencies (cm.$^{-1}$) of diacetylamino-compounds as liquid films or Nujol mulls.*

NN-Diacetyl-	ν (cm.$^{-1}$)	*NN*-Diacetyl-	ν (cm.$^{-1}$)
Benzylamine [a]	1727 (sh), 1718, 1701	*m*-Toluidine [a]	1730 (broad), 1715 (broad), 1706 (sh)
1-Naphthylamine [b]	1727, 1706		
2-Naphthylamine [b]	1727 (sh), [e] 1712 (broad)	*p*-Toluidine [a]	1727, 1720, 1706 (sh)
Aniline [a, c]	1724 (sh), 1712, 1701 (sh) [e]	*o*-Anisidine [a]	1728, 1720, 1704 (sh)
Aniline [a, d]	1724 (sh), 1709 (sh), 1701	*p*-Anisidine [a]	1728, 1718, 1709 (sh) [e]
o-Toluidine [a]	1733, 1720, 1689 (sh)m	*p*-Anisidine [b]	1730, 1712

All the extinction coefficients are high. Slit schedule 1·5 mm. (except for diacetylaniline). [a] Liquid film. [b] Nujol mull. [c] Slit schedule 1 mm. [d] Slit schedule 0·5 mm. [e] Not very well defined shoulder.

2-*Acetyl*-1 : 2 : 3 : 4-*tetrahydro*-7-*methoxy*-9-*methyl*-1-*oxo*-β-*carboline*.—Prepared as above from the oxocarboline,[1] the *acetyl derivative* formed colourless rods, m. p. 162° (Found: C, 65·8; H, 6·1. $C_{15}H_{16}O_3N_2$ requires C, 66·2; H, 5·9%), from alcohol.

2-*Acetyl*-1 : 2 : 3 : 4-*tetrahydro*-8-*methyl*-1-*oxo*-β-*carboline*, m. p. 146—147°, was similarly

[7] Sudborough, *J.*, 1901, **79**, 533.
[8] Holmes and Ingold, *J.*, 1925, **127**, 1800.
[9] Suida, *Ber.*, 1879, **12**, 1327.

obtained as pale yellow needles from alcohol (Found : C, 68·9; H, 5·8. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8%).

Infrared Spectra.—A Grubb-Parsons double-beam spectrometer, type S4, with a sodium chloride prism was used. The frequency scale was calibrated by ammonia vapour bands (accuracy ±5 cm.$^{-1}$ in the 6 μ region). "AnalaR" chloroform was used. The measurements on mulls and liquid films were carried out with a slit schedule of 1·5 mm. (except for diacetylaniline, when measurements were carried out at slit schedules of 1 mm. and 0·5 mm.).

TABLE 3. *Carbonyl frequencies (cm.$^{-1}$) of chloroform solutions of diacetylamines. Effect of altering slit schedule and concentration (constant cell thickness of 0·01 in.).*

	Slit schedule 1·5 mm.		Slit schedule 0·5 mm.	
NN-Diacetyl-	50 mg./c.c.	10 mg./c.c.	50 mg./c.c.	10 mg./c.c.
Benzylamine ...	1718 s, 1701 s	1709 s	1727 (sh)m, 1709 (sh)s, 1689 s	1727 (sh)w, 1712 (sh)ms, 1698 s, 1686 (sh)m
1-Naphthylamine	1739 (sh)s, 1727 s	1724 s	1727 (sh)s, 1706 (sh)s, 1698 s	1727 (sh)m, 1709 s, 1701 (sh)m
2-Naphthylamine	1730 (sh)s, 1718 s	1721 s	1730 (sh)m, 1709 (sh)s, 1701 s	1727 (sh)m, 1709 s, 1701 (sh)s
Aniline	1721 (sh)s, 1709 s (broad)	1718 s	1727 (sh)ms, 1706 (sh)s, 1695 s	1724 (sh)m, 1704 s, 1698 (sh)s
o-Toluidine	1727 s, 1712 s (broad)	1718 s	1727 (sh)m, 1706 (sh)s, 1701 s	1727(sh)m, 1709 s, 1701 (sh)s
m-Toluidine	1733 s, 1718 s (broad)	1718 s	1727 (sh)s, 1709 (sh)s, 1695 s	1727 (sh)m, 1709 s, 1701 (sh)s
p-Toluidine	1727 (sh)s, 1709 s (broad)	1718 s	1724 (sh)m, 1704 (sh)s, 1692 s	1727 (sh)w, 1706 s, 1701 (sh)s
o-Anisidine	1727 (sh)s, 1718 s (broad)	1718 s	1727 (sh)ms, 1709 (sh)s, 1701 s	1727 (sh)m, 1709 s, 1701 (sh)s
p-Anisidine	1727 (sh)s, 1715 s (broad)	1718 s	1727 (sh)ms, 1706 (sh)s, 1698 s	1727 (sh)m, 1706 s, 1701 (sh)s

TABLE 4. *Amide carbonyl frequencies (cm.$^{-1}$) of chloroform solutions of some diacylamines. Effect of dilution (variable cell thickness).*

Compound	Slit schedule (mm.)	Concn. (mg./c.c.)	Cell thickness (in.)	ν
NN-Diacetyl-1-naphthylamine	0·5	100	0·0025	1724 (sh)m 1698 s 1686 (sh)s
	0·5	50	0·005	1724 (sh)m 1701 s 1692 (sh)s
	0·5	10	0·025	1724 (sh)m 1701 s 1692 (sh)s
	1·5	100	0·0025	1724 (sh)s 1715 s
	1·5	50	0·005	1724 (sh)s 1712 s
	1·5	10	0·025	1715 s
NN-Diacetyl-*p*-anisidine	0·5	50	0·005	1724 (sh)m 1701 s 1692 (sh)s
	0·5	10	0·025	1724 (sh)m 1701 s 1686 (sh)s
	1·5	50	0·005	1715 s
	1·5	10	0·025	1715 s

Chloroform solution spectra were measured at slit schedules of both 1·5 mm. and 0·5 mm. to obtain better resolution. A variable-path cell was used to study the effect of dilution, *e.g.*, when the concentration of the solution was halved the cell-thickness was doubled.

The results are summarised in Tables 2, 3, 4, and 5; abbreviations have their usual meanings (sh = shoulder).

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TABLE 5. *Amide carbonyl frequencies (cm.$^{-1}$) of miscellaneous diacylamino-compounds. (Slit schedule 1·5 mm.)*

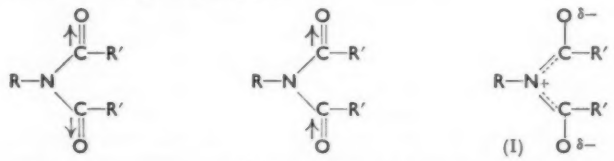
Compound	ν	Compound	ν
N-Acetyloxindole [a]	1770 s 1689 s	Succinimide [a]	1786 s 1727 (sh)s
N-Acetyloxindole [b]	1770 s 1689 s	Succinimide [b]	1715 s broad 1786 mw
2-Acetyl-1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline [a]	1701 s 1672 s		1764 m 1730 s
2-Acetyl-1 : 2 : 3 : 4-tetrahydro-9-methyl-1-oxo-β-carboline [a]	1701 (sh)s [c] 1686 s	*N*-Bromosuccinimide [a]	1783 m 1727 (sh)
2-Acetyl-1 : 2 : 3 : 4-tetrahydro-7-methoxy-9-methyl-1-oxo-β-carboline [a]	1686 s broad 1672 (sh)s	*N*-Bromosuccinimide [b]	1709 s broad 1783 (sh) vw 1733 s
2-Acetyl-1 : 2 : 3 : 4-tetrahydro-8-methyl-1-oxo-β-carboline [a]	1695 s 1675 s	*N*-Bromosuccinimide [b,d]	1730 (sh)m 1721 s 1715 (sh)s 1698 (sh)m

[a] Nujol mull. [b] Dilute chloroform solution. [c] Not very well defined shoulder. [d] Slit schedule 0·5 mm.

DISCUSSION

In all the compounds examined at least two bands appear in the 6 μ region, both of which can be attributed to amide carbonyl stretching vibrations. In many cases some of the bands only appear as shoulders and these may not be very well defined. Also, as can be seen from Table 3 (column 2) when very dilute chloroform solutions are used, with slit schedules of 1·5 mm., the diacetylanilines exhibit a single strong sharp peak at 1718 cm.$^{-1}$, though this can be resolved into its component bands by using narrower slit schedules, as the data in the last column of Table 3 show. The possible symmetry effect, mentioned in connection with the data in Table 1, does not, in fact, exist and it seems probable that all *NN*-diacylamino-compounds exhibit doublets for the amide absorption if examined at sufficiently slow chart speeds and narrow enough slit schedules. Thus, contrary to report,[3] *N*-bromosuccinimide shows more than one carbonyl band in the region (Table 5).

The measurements in chloroform solution rule out the possibility that the multiplicity of bands could be due to association in the condensed state. This is even better illustrated in the dilution experiments carried out with *NN*-diacetyl-1-naphthylamine and diacetyl-*p*-anisidine (these compounds were chosen because of the very well-defined bands they show in the solid state) and by varying the path length in inverse ratio to the dilution (Table 4), when no change, in either position or apparent intensity of the bands, is observed. This is in agreement with the results obtained by Hunter and Reynolds [10] who showed, by cryoscopic measurements on various diacylamines, that when no imido-hydrogen is present molecular association is completely suppressed.



(I)

There seems to be no reason to attribute either of the bands to a specific carbonyl group, as has been done [2] in the cases of the succinimides, for instance. It appears more likely that this multiplicity of bands is a further example of the more general case of vibrational coupling between carbonyl groups [11] of which diacyl and diaroyl peroxides and acid anhydrides are others. The main bands observed could, for instance, be attributed

[10] Hunter and Reynolds, *J.*, 1950, 2857.
[11] Jones and Sandorfy, "Technique of Organic Chemistry. Vol. IX. Chemical Applications of Spectroscopy," Interscience, London, 1956, p. 495.

to symmetrical and unsymmetrical vibrational coupling of the two carbonyl groups. In the symmetrical acid anhydrides the bands may be separated by 65 cm.$^{-1}$ compared with 20—30 cm.$^{-1}$ in symmetrical peroxides.[11] In the mixed diacylamines there is more justification for attributing the separate bands to the individual amide carbonyl groups, since the difference in the fundamental stretching frequency of the two carbonyl groups will make coupling between these groups less likely.

As has already been noted,[4-6] the C=O absorption in *NN*-diacetyl derivatives is at higher frequencies than the C=O absorption in the corresponding monoacetyl compound. This is in agreement with the effect of the presence of electrophilic groups on the nitrogen atom [12] which increase the double-bond character of the carbonyl group and also with the fact that the effect of the positive charge on the nitrogen atom in the dipolar form is shared between the two acetyl groups (I), with the same result. The appearance of a doublet in this region, together with the absence of NH bands in the 3 μ region, can then be used to distinguish between diacetyl- and monoacetyl-amino-derivatives, as suggested by Grove, Jeffs, and Rustidge.[4]

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STRAND, LONDON, W.C.2. [*Received, October 29th*, 1956.]

[12] Richards and Thompson, *J.*, 1947, 1248.

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267. *Cyclitols. Part IV.* Methyl Ethers of* myo*Inositol.*†

By S. J. ANGYAL, P. T. GILHAM, and (in part) C. G. MACDONALD.

Dambonitol is shown to be 1 : 3-di-*O*-methyl*myo*inositol and bornesitol to be one of the enantiomers of the 1-methyl ether. Methylation of *myo*-inositol has given the (±)-1- and the 2-methyl derivative. Dambonitol acetate has been synthesised by methylation of 1 : 4 : 5 : 6-tetra-*O*-acetyl-*myo*inositol which is accompanied by acetyl migration.

*myo*INOSITOL (I) can give rise to four structurally different monomethyl ethers: the symmetrical 2- and 5-compound and the resolvable 1- and 4-derivative. Three of these ethers have so far been found in Nature: the inactive sequoyitol, the dextrorotatory ononitol, and bornesitol which occurs in both enantiomorphous forms. Several synthetic monomethyl ethers have also been reported. Two dimethyl ethers, the inactive dambonitol and the active liriodendritol, have been isolated from natural sources. The present paper discusses the structure of these compounds except that of the very recently described liriodendritol.[2]

Sequoyitol occurs in the heartwood of *Sequoia sempervirens*,[3] in the sugar pine [4] (*Pinus lambertiana*), and in *Macrozamia riedlei*.[5] Anderson *et al.*[6] have shown that sequoyitol is 5-*O*-methyl*myo*inositol and we have confirmed this conclusion by a synthesis which will be reported in a subsequent publication. Foster,[7] using a sample of sequoyitol isolated from *Macrozamia riedlei* by Riggs, found that it gave two spots on paper ionophoresis in borate buffer and suggested that both the 2- and the 5-methyl ether were present. Our sample, also a generous gift from Dr. Riggs, showed the same behaviour

* Part III, *J. Amer. Chem. Soc.*, 1955, **77**, 4343.

† The prefix *myo* is used [1] instead of the older, non-specific *meso*, to describe the 1 : 2 : 3 : 5/4 : 6-inositol.

[1] Fletcher, Anderson, and Lardy, *J. Org. Chem.*, 1951, **16**, 1238.
[2] Plouvier, *Compt. rend.*, 1955, **241**, 765.
[3] Sherrard and Kurth, *J. Amer. Chem. Soc.*, 1929, **51**, 3139.
[4] Anderson and Ballou, *ibid.*, 1953, **75**, 648.
[5] Riggs, *J.*, 1949, 3199; *Austral. J. Chem.*, 1954, **7**, 123.
[6] Anderson, Deluca, Bieder, and Post, *J. Amer. Chem. Soc.*, in the press.
[7] Foster, *Chem. and Ind.*, 1953, 592.

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but we found that the second spot was due to an impurity, macrozamin; after purification it was ionophoretically homogeneous and identical with a sample of Sherrard and Kurth's original sequoyitol [3] (obtained by the courtesy of Dr. A. J. Stamm).

(+)-Bornesitol was isolated from " Borneo rubber " by Girard,[8] from commercial rubber of unidentified origin by Flint and Tollens,[9] and, more recently, from opepe wood; [10] the (−)-isomer has also been found [11] in Nature. An attempt to find the " Borneo rubber " led us to *Dyera lowii*, the only latex-producing tree which is nowadays tapped in Borneo; however, it was found to contain dambonitol (see below). Foster and Stacey [12] have claimed that bornesitol is one of the enantiomers of 1-*O*-methyl*myo*inositol because its ionophoretic mobility in borate buffer is much less than that of *myo*inositol; this was taken as evidence that one of the pairs of *cis*-hydroxyl groups is blocked by the methyl group. It was later found,[7] however, that sequoyitol—with all its *cis*-hydroxyls free—also moves much more slowly than *myo*inositol; and that some cyclitols devoid of *cis*-1 : 2-diol groups show ionophoretic mobility.[13] Foster and Stacey's argument is therefore not conclusive; nevertheless, as will be shown in this paper, the 1-*O*-methyl structure postulated by them is correct.

Ononitol has recently been isolated by Plouvier; [11] since it is optically active it must be one of the enantiomers of 4-*O*-methyl*myo*inositol. This conclusion has been confirmed by the synthesis of its racemate (to be reported later).

An obvious way of preparing a structurally well-defined methyl ether would be by the methylation of 1 : 3 : 4 : 5 : 6-penta-*O*-acetyl*myo*inositol.[14] Our experiments, using methyl iodide and silver carbonate, failed to introduce a methyl group into this compound. Employing silver oxide and a higher temperature, Anderson and Landel [15] obtained a methyl ether which, however, proved to be structurally identical with bornesitol. Apparently, under the effect of the alkaline silver oxide, acetyl migration occurred setting up an equilibrium between two penta-acetates, and the equatorial 1-hydroxyl group of the one was methylated in preference to the axial 2-hydroxyl group of the other.

Preparation of a methyl ether by direct methylation of *myo*inositol was described by Griffin and Nelson.[16] Repetition of their experiments gave a complex mixture from which two monomethyl ethers were isolated in poor yield. One isomer, m. p. 200°, presumably identical with Griffin and Nelson's compound, m. p. 204°, has been shown to be structurally identical with bornesitol by comparison of their R_F values in four solvent systems, of their ionophoretic mobility in borate buffer, and of the infrared spectra of their penta-acetates. The infrared spectrum of each penta-*O*-acetyl-*O*-methyl*myo*inositol is different. This isomer is therefore the racemate of bornesitol, (±)-1-*O*-methyl*myo*inositol; it was identical with Anderson and Landel's methyl ether.[15] The other isomer, m. p. 237°, had an infrared spectrum and ionophoretic mobility different from those of sequoyitol, bornesitol, and ononitol; it must therefore be the 2-methyl ether. All the structurally possible monomethyl ethers of *myo*inositol are therefore now known.

At the time these experiments were performed (1951) the separations were carried out by fractional crystallisations and we made no use yet of chromatography. Later, sequoyitol was isolated from one of the fractions by chromatography on cellulose powder.

Dambonitol, which occurs in a variety of latex-producing trees, has recently been isolated from *Dyera costulata* and *D. lowii* by Comollo and Kiang [17] and, independently, by us. Comollo and Kiang proposed the 2 : 5-dimethyl structure, for they found that

[8] Girard, *Compt. rend.*, 1871, **73**, 426.
[9] Flint and Tollens, *Annalen*, 1892, **272**, 288.
[10] King and Jurd, *J.*, 1953, 1192.
[11] Plouvier, *Compt. rend.*, 1955, **241**, 983.
[12] Foster and Stacey, *Chem. and Ind.*, 1953, 279.
[13] Angyal and McHugh, following paper.
[14] Iselin, *J. Amer. Chem. Soc.*, 1949, **71**, 3822; May, *J. Org. Chem.*, 1952, **17**, 286.
[15] Anderson and Landel, *J. Amer. Chem. Soc.*, 1954, **76**, 6130.
[16] Griffin and Nelson, *ibid.*, 1915, **37**, 1552.
[17] Comollo and Kiang, *J.*, 1953, 3319.

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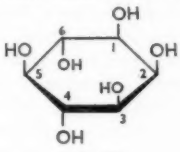
dambonitol would not react with acetone and that it consumed two mols. of periodate without the production of formic acid. After communication of our conflicting results to them, Kiang and Loke [18] re-investigated the periodate oxidation and found that one mol. of formic acid was produced, albeit slowly. Similar results were obtained by Anderson and Drummond.[19] The periodate oxidation indicates a *m*-dimethoxy-structure, and Kiang and Loke concluded that dambonitol is the 1 : 3-dimethyl ether. Their proof, however, depends on negative evidence, *i.e.*, that an *iso*propylidene compound was not obtained; in view of the slowness of the reaction of *myo*inositol with acetone (see below), this cannot be regarded as definite proof for the absence of a *cis*-1 : 2-glycol system.



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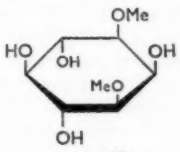
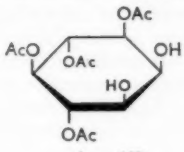


(II)



(III)

Dambonitol shows no ionophoretic mobility in 0·15M-borate buffer. This is evidence for the absence of *cis*-1 : 2-diol groups since all cyclitols possessing such a group move under these conditions.[13] Dambonitol must therefore have one methoxyl group on $C_{(2)}$ or the two methoxyl groups on $C_{(1)}$ and $C_{(3)}$. Partial demethylation gave *only one* monomethyl ether, (±)-bornesitol. These facts, taken in conjunction with the *meso*-nature of the compound and the evidence from periodic acid oxidations, prove that dambonitol is 1 : 3-di-*O*-methyl*myo*inositol (II); bornesitol is therefore one of the enantiomers of 1-*O*-methyl*myo*inositol.

Subsequently, dambonitol has been synthesised by the methylation of 1 : 4 : 5 : 6-tetra-*O*-acetyl*myo*inositol [20] (III). It was assumed that, as in the methylation of the penta-acetyl compound, acetyl migration will occur and the equatorial hydroxyl groups will be methylated in preference to the axial one. Dambonitol acetate was indeed found to be the main product of the reaction; besides this, after deacetylation, 1- and 2-*O*-methyl*myo*inositol were isolated and a small amount of another dimethyl ether, presumably the 1 : 2-isomer. Absence of the other monomethyl ethers in the mixture indicates that acetyl migration occurred only between *cis*-related hydroxyl groups.

1 : 4 : 5 : 6-Tetra-*O*-acetyl*myo*inositol (III) was prepared by mild hydrolysis of 1 : 4 : 5 : 6-tetra-*O*-acetyl-2 : 3-*O*-*iso*propylidene*myo*inositol. The preparation of the latter described previously [20,21] was improved by the use of very large amounts (up to 40%) of zinc chloride dissolved in acetone; but even under these vigorous conditions the reaction of *myo*inositol with acetone is much slower than that of other cyclitols. This effect is undoubtedly due to the unfavourable conformation of three contiguous *cis*-hydroxyl groups.[13]

In the paper-chromatographic characterisation of *O*-methylinositols it was noticed that all the naturally occurring ethers were contaminated by the parent inositol, which was not usually removed by recrystallisation but very effectively by chromatography on cellulose powder.[4] Thus King's bornesitol, Riggs's sequoyitol, and Plouvier's ononitol contained some *myo*inositol. Quebrachitol contained both *myo*- and (−)-inositol.[22] In the sugar pine, pinitol and sequoyitol are accompanied by (+)- and *myo*inositol.[4] It appears that the inositols are intermediates in the biosynthesis of their methyl ethers. Significantly, in both *Dyera* species dambonitol is accompanied by a monomethyl ether and by traces of *myo*inositol. The former was isolated by chromatography on cellulose powder and was identified as (+)-bornesitol, the intermediate in a step-wise methylation.

[18] Kiang and Loke, *J.*, 1956, 480.
[19] Dr. L. Anderson, personal communication, Aug. 1954.
[20] Dangschat, *Naturwiss.*, 1942, **30**, 146.
[21] Angyal and Macdonald, *J.*, 1952, 686.
[22] Smith, *Biochem. J.*, 1954, **57**, 140.

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It is of interest that all the monomethyl ethers of *myo*- and the optically active inositols in which the methoxyl group is equatorial have been encountered in Nature, but none of those with an axial methoxyl group; the enzymes responsible for methylation apparently avoid the steric strain caused by bulky axial groups. The two methoxyl groups in dambonitol are also equatorial.

Experimental

M. p.s are corrected.

Cellulose-powder Chromatography.—Whatman cellulose powder (standard grade) was mixed to a thin paste with acetone–water (4 : 1 v/v) and stirred for 5 min. in a Waring blendor. The mixture was then poured, in small portions, into a chromatographic column already containing some 1 : 4-aqueous acetone, and allowed to settle without stirring, tapping, or compression. Each addition was made before the cellulose previously added had fully settled; the tap at the bottom of the column was fully opened but the column never allowed to run dry. Columns thus prepared could be used many times as long as they were kept covered with solvent. The surface of the packing was protected by a filter-paper disc. The mixture to be chromatographed was introduced in the minimum amount of water, diluted with 4 vols. of acetone (or with as much as could be added without causing precipitation). A drop of methyl-orange (R_F 1·0) was added to mark the solvent front: no fractions were collected until the dye appeared in the effluent. Lissamine-red 6BS (R_F 0·35) is a convenient aid in showing the progress of the elution; the dyes also show at a glance whether the packing of the column is faulty. Acetone–water (4 : 1 v/v) was used as the moving phase in all experiments.

Methylation of myo*Inositol.*—A solution of *myo*inositol (50 g.) and barium hydroxide octahydrate (320 g.) in water (750 ml.) was stirred under reflux while dimethyl sulphate (125 g.) was added during 1½ hr. After a further 6 hours' boiling, the mixture was acidified with 10N-hydrochloric acid and filtered with the aid of kieselguhr. The solid was extracted with boiling water (600 ml.), and the extract combined with the filtrate and evaporated to dryness. The residue was extracted with boiling ethanol (2 × 250 ml.).

The undissolved material (115 g.) was remethylated and the process repeated twice more, with decreasing amounts of barium hydroxide and dimethyl sulphate. The undissolved material (22 g.) then contained less than 2 g. of acetylatable substance.

The combined ethanolic extracts deposited a solid (7·5 g.) containing considerable amounts of *myo*inositol. The mother-liquors were evaporated and acetylated with acetic anhydride and sulphuric acid; the acetyl derivatives were stirred to a paste with ethanol and filtered, giving a solid (30 g.) and, on evaporation of the ethanol, a syrup (13 g.).

The solid was fractionally crystallised from water. The least soluble material (1·5 g.; m. p. 220—225°) was *penta*-O-*acetyl*-2-O-*methyl*myo*inositol.* Several recrystallisations from ethanol, and then from ethyl acetate, raised the m. p. to 235—236° (Found: C, 50·5; H, 5·95. $C_{17}H_{24}O_{11}$ requires C, 50·5; H, 6·0%).

The next fraction (7 g.; m. p. 140—145°) gave (±)-penta-*O*-acetyl-1-*O*-methyl*myo*inositol (5·8 g.; m. p. 147—148°) on crystallisation from water (500 ml.). Repeated crystallisation from ethanol raised the m. p. to 152—153° (Griffin and Nelson [18] give m. p. 141°; Anderson and Landel,[18] m. p. 154—154·5°), mixed m. p. with Anderson's sample, 152—153°.

A later fraction, m. p. 125—140°, was deacetylated and chromatographed on cellulose powder, giving sequoyitol (m. p. 239°), 1-*O*-methyl*myo*inositol (m. p. 200°), and *myo*inositol. The dimethyl ether described by Griffin and Nelson [16] was not encountered in our work.

2-O-*Methyl*myo*inositol.*—Deacetylation of the acetate with dry methanol containing a trace of sodium methoxide and crystallisation from ethanol gave the *methyl ether*, m. p. 212° (Found: C, 43·4; H, 7·1. $C_7H_{14}O_6$ requires C, 43·3; H, 7·25%).

(±)-1-O-*Methyl*myo*inositol.*—Deacetylation of the acetate and crystallisation from aqueous ethanol gave the methyl ether, m. p. 199—200° (lit.,[15,16] m. p. 200—201°, 204°), mixed m. p. with Anderson's sample, 200—201°; with bornesitol, 191—194° (Found: C, 43·1; H, 7·2%).

The ionophoretic behaviour of these compounds is reported elsewhere.[13]

Purification of Sequoyitol.—Riggs's crude sequoyitol was crystallised several times from aqueous ethanol until the m. p. rose to 236—237°. Admixture of Sherrard and Kurth's "sequoyite" [3] caused no lowering of the m. p. (This material still contains some inositol: chromatographically pure sequoyitol melts at 239°.) The combined mother-liquors were evaporated to dryness and extracted three times with ethanol; from water–ethanol (2 : 5) the

insoluble residue gave large crystals which melted, alone and on admixture with macrozamin, at 202—203°. The R_F value (0·44 in 80% acetone) was the same as that of macrozamin.

Infrared Spectra of the Methylinositol Acetates.—To avoid any differences caused by crystal structure, the spectra were taken on 6% solutions in $CHCl_3$ with a Perkin-Elmer Model 12C instrument and a rock-salt prism.

Absorption bands were found at the following frequencies:

Penta-*O*-acetylbornesitol and -(±)-1-*O*-methyl*myo*inositol: 904(m), 921(w), 950(s), 968(w), 983(w), 1037(s), 1068(s), 1087(w), 1120(w), 1128(m), and 1163(w).

Penta-*O*-acetyl-2-*O*-methyl*myo*inositol: 911(w), 930(m), 946(w), 979(m), 1040(s), 1122(m), and 1172(w).

Penta-*O*-acetylononitol: 902(w), 921(w), 947(m), 978(m), 1035(s), 1055(s), 1084(w), 1100(w), 1113(w), and 1148(w).

Penta-*O*-acetylsequoyitol: 915(w), 951(s), 1066(m), 1093(w), 1139(w), and 1167(m).

Dambonitol from Dyera costulata.—Jelutong (*D. costulata*) latex (1·5 gallons) was coagulated by addition of phosphoric acid in the Timber Research Laboratory, Kuala Lumpur; the serum (1 l.) was shipped to Sydney. On arrival, it was neutralised with concentrated ammonia solution (25 ml.), filtered from some gelatinous precipitate, refiltered with charcoal, and evaporated to dryness *in vacuo*. The residue, crystallised from ethanol, gave two crops (45 and 12 g.) of dambonitol, m. p. 204—206°. Recrystallisation from ethanol (650 ml.) gave large crystals (50 g.), m. p. 206—207°, of dambonitol (lit.,[17] m. p. 210°); paper chromatography in 80% acetone showed the presence of bornesitol and *myo*inositol. Contrary to the statement of Comollo and Kiang [17] dambonitol is not hygroscopic. It was recovered unchanged after attempts to condense it with acetone [21] or to oxidise it by *Acetobacter suboxydans*.

To isolate the bornesitol, crude dambonitol (3 g.) was recrystallised from ethanol (30 ml.), and the solid residue (0·6 g.) left by evaporating the mother-liquor was chromatographed on a 1¼ in. × 9 in. cellulose-powder column; 10 ml. fractions were collected. Fractions 23—34, which paper chromatography showed to contain predominantly methylinositol, gave 40 mg. of solid which, on slow crystallisation from aqueous ethanol, yielded dextrorotatory crystals (20 mg.), m. p. 202—203°; mixed m. p. with bornesitol, 203°; with (±)-1-*O*-methyl*myo*inositol, 191—193°.

Dambonitol from D. lowii.—The latex was treated with phosphoric acid by natives in the Borneo jungle and the resulting coagulum pressed as dry as possible at the Chicle Development Co., Bintulu. The serum (250 ml.), which smelt strongly of butyric acid when received in Sydney, was concentrated to 25 ml., an equal volume of ethanol added and the mixture filtered with charcoal. Evaporation of the filtrate left a gum (2·3 g.) which was dissolved in water (8 ml.). Addition of ethanol (24 ml.) gave a gummy precipitate which was separated by filtration. The filtrate was evaporated and the residue chromatographed through cellulose powder: 10 ml. fraction were collected. Fractions 7—15 (1·3 g. of solid) gave dambonitol (0·8 g.), m. p. 203—204°, on crystallisation from ethanol. Repeated crystallisation raised the m. p. to 208°; paper chromatography showed no bornesitol or inositol. The tetra-acetate, prepared by treatment with acetic anhydride and pyridine for 1 hr. at 100° and crystallisation from aqueous ethanol, melted at 202° (lit.,[17] 195°). From fractions 16—23 (66 mg. of solid) a few crystals of bornesitol were isolated; in later fractions the presence of *myo*inositol was shown by paper chromatography.

Partial Demethylation of Dambonitol.—Dambonitol (500 mg.) and concentrated hydriodic acid (1 ml.) were heated on a steam-bath for 15 min. The mixture was evaporated to dryness in a desiccator over sodium hydroxide, and the residue dissolved in water and extracted with chloroform to remove iodine. The concentrated aqueous layer was then placed on a cellulose-powder column. Fractions 5—9 (120 mg.) contained mainly dambonitol, and fractions 23—30 (70 mg.) mainly *myo*inositol. Fractions 10—18 all showed a spot at R_F 0·32 and were evaporated together (220 mg.): addition of ethanol and filtration gave crystals, m. p. 196—200°, mixed m. p. with (±)-1-*O*-methyl*myo*inositol, 198—200°. Acetylation with acetic anhydride and sulphuric acid, followed by crystallisation from ethanol, gave (±)-penta-*O*-acetyl-1-*O*-methyl-*myo*inositol, m. p. 150—152°, mixed m. p. 151—152°.

(±)-3 : 4 : 5 : 6-*Tetra*-O-*acetyl*-1 : 2-O-iso*propylidene*myo*inositol*.—The previously described preparation [20, 21]—reaction of *myo*inositol with acetone containing zinc chloride and acetic acid—proved unreliable and a better method has been developed. The main difficulty was thought to be the low solubility of inositol in the reaction mixture; it was subsequently found

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that inositol could be dissolved in acetone containing very large amounts of zinc chloride, presumably by complex formation. Acetic acid had to be omitted, however, otherwise extensive acetylation occurred. Under these conditions, the reaction of *myo*inositol with acetone was reproducible but still very slow: half of the inositol was unchanged after 50 hours' refluxing.

Finely powdered anhydrous *myo*inositol (10 g.), anhydrous zinc chloride (80 g.), and dry acetone (200 ml.) were heated under reflux for 40 hr. Dry acetone (200 ml.) was added and the heating continued for another 10 hr. Dry pyridine (200 ml.) was added to the cooled mixture and, after a few hours at 0°, the precipitated pyridine–zinc chloride complex was filtered off and washed with a little acetone. The combined filtrates were mixed with acetic anhydride (100 ml.) and heated on a steam-bath until most of the acetone had evaporated. After a further hour's heating, the mixture was cooled, mixed with chloroform (100 ml.), and diluted with water. The chloroform layer was washed several times with sodium carbonate solution, dilute hydrochloric acid, and water. After drying (Na_2CO_3), the chloroform was evaporated and the residual oil was triturated with light petroleum (100 ml.). The crystals (7·0 g.) which formed were filtered off and recrystallised from ethanol, to give colourless prisms (6·4 g.), m. p. 122—123° (lit.,[20] 123—124°).

Unchanged inositol was recovered as its hexa-acetate (11 g.) by acetylating the pyridine–zinc chloride complex with acetic anhydride and pyridine. Thus the yield of the *iso*propylidene derivative was 60% based on unrecovered inositol.

(±)-1 : 4 : 5 : 6-*Tetra*-O-*acetyl*myo*inositol* (III).—The above tetra-acetate (4·0 g.) was heated with 80% acetic acid (20 ml.) on the steam-bath for 1 hr. The solution was evaporated *in vacuo*, redissolved in water, and again evaporated. The residual resin crystallised from water, yielding colourless prisms of the hydrated tetra-acetate which, after drying for 3 hr. at 80° and then at 100° *in vacuo*, weighed 2·77 g. (77%) and melted at 139°. Further crystallisation raised the m. p. to 142—143° (Found: C, 48·4; H, 5·9. Calc. for $C_{14}H_{20}O_{10}$: C, 48·3; H, 5·8%). Dangschat [20] gives the m. p. as 132—133° and states that 3 : 4 : 5 : 6-tetra-*O*-acetyl-1 : 2-*O*-*iso*propylidene*myo*inositol is *not* hydrolysed by acetic acid.

Methylation of 1 : 4 : 5 : 6-*Tetra*-O-*acetyl*myo*inositol* (III).—The above acetate (0·5 g.), methyl iodide (20 ml.), dioxan (30 ml.), and freshly prepared silver oxide [23] (5 g.) were refluxed for 60 hr. Paper chromatography of a hydrolysed sample showed much dimethyl ether besides small amounts of monomethyl ether and inositol. The mixture was filtered and evaporated; the residue was dissolved in hot aqueous ethanol and gave crystals (0·29 g.) on cooling. Several crystallisations from water yielded tetra-*O*-acetyldambonitol (70 mg.), m. p. and mixed m. p. 202° (Found: C, 51·25; H, 6·3. Calc. for $C_{16}H_{24}O_{10}$: C, 51·05; H, 6·45%).

The combined mother-liquors were evaporated, hydrolysed with hydrochloric acid, and evaporated, and the residue (0·17 g.) was chromatographed over cellulose powder; 10 ml. fractions were collected. Fractions 20—30 gave an oil (35 mg.) from which, by three crystallisations from ethyl acetate, plates of (presumably) 1 : 2-*di*-O-*methyl*myo*inositol*, m. p. 162—163°, were obtained (Found: C, 46·5; H, 7·7. $C_8H_{16}O_6$ requires C, 46·15; H, 7·75%).

Fractions 31—40 contained 18 mg. which, after two crystallisations from ethanol, gave 2-*O*-methyl*myo*inositol, m. p. and mixed m. p. 210—211°. Fractions 41—60 contained 25 mg. which gave, by crystallisation from ethanol, 1-*O*-methyl*myo*inositol, m. p. and mixed m. p. 198—200°. Fractions 80—100 contained *myo*inositol.

Methylation with silver carbonate instead of silver oxide gave similar results.

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[23] Bates *et al.*, "Polarimetry, Saccharimetry and the Sugars," Nat. Bur. Stand., Circular C440, Washington, 1942, p. 507.

268. *Cyclitols. Part V.* Paper Ionophoresis, Complex Formation with Borate, and the Rate of Periodic Acid Oxidations.*

By S. J. Angyal and D. J. McHugh.

The ionophoretic mobilities of some 29 cyclitols and related compounds have been determined in sodium tetraborate solutions. In many cases the values are not related to the presence or to the number of *cis*-1 : 2-diol groups, which have always been regarded as necessary for complex formation. In these cases, mobilities are caused by 1 : 1 complexes formed from boric acid and cyclitols which contain *cis*-1 : 3 : 5-hydroxyl groups; the tridentate structure (IV) is assigned to these complexes. Equilibrium constants of complex formation, and the acid dissociation constant of one tridentate complex (that of *cis*inositol), have been determined.

The initial rate of the reaction between cyclitols and periodic acid is found to vary considerably with configuration. It is suggested that the presence of steric strain explains the very fast reaction of several cyclitols.

Cyclitols, like other polyhydroxy-compounds,[1-5] show ionophoretic mobility in aqueous sodium borate solution.[6] As an alternative to paper chromatography, paper ionophoresis is useful in the identification and characterisation of cyclitols and their derivatives, *e.g.*, the methyl ethers of *myo*inositol (I) have very similar R_F values [7] but differ in their ionophoretic mobility.

Every inositol, except the all-*trans-scyllo*-isomer, has a high ionophoretic rate of migration (expressed as M_G, the movement relative to that of glucose [4]) and the various isomers are not well separated in 0·15M-borax solution. It was found, however, that approximately ten-fold dilution of the electrolyte changed the M_G values considerably, reversing their order in some cases, causing wide separation of the inositols, and at the same time improving the sensitivity of their detection. On the other hand, some of the slower-moving compounds showed no mobility at the greater dilution. The M_G values, in sodium tetraborate solutions of two different concentrations, of all the inositols, of the known quercitols and inositol methyl ethers, and of some related compounds are given in Table 1, together with Foster's values.[6b]

Ionophoretic mobility has been used by Foster and Stacey [6a] to deduce the likely structure of cyclitols. Complex formation with borate is generally believed to involve *cis*-1 : 2-diol structures.[8] (Frahn and Mills have shown [9] that some aliphatic 1 : 3-diols have ionophoretic mobility, but we have found no migration of *cis-cyclo*hexane-1 : 3-diol, or of *trans-cyclo*hexane-1 : 2 : 3-triol; complex formation with *cis*-1 : 3-hydroxyl groups is therefore not significant in the ionophoresis of *cyclo*hexane derivatives.) Foster and Stacey [6] have postulated that higher M_G values indicate a larger number of *cis*-1 : 2-diol groups; this assumption, however, did not prove generally valid. Foster's M_G value [6b] for sequoyitol (5-*O*-methyl*myo*inositol)—much lower than that for *myo*inositol (I), although both compounds possess the same three contiguous *cis*-hydroxyl groups—appeared anomalous. The present results reveal numerous anomalies, particularly in the more dilute electrolyte. Thus, sequoyitol and ononitol, each with three adjacent *cis*-hydroxyl

* Part IV, preceding paper.

[1] Consden and Stanier, *Nature*, 1952, **169**, 783.
[2] Kowkabany, *Adv. Carbohydrate Chem.*, 1954, **9**, 338.
[3] Foster, *Chem. and Ind.*, 1952, 828.
[4] *Idem*, *J.*, 1953, 982.
[5] Foster and Stacey, *J.*, 1955, 1778.
[6] (*a*) *Idem*, *Chem. and Ind.*, 1953, 279; (*b*) Foster, *ibid.*, p. 951.
[7] Angyal, Gilham, and McHugh, following Note.
[8] Böeseken, *Adv. Carbohydrate Chem.*, 1949, **4**, 189.
[9] Frahn and Mills, *Chem. and Ind.*, 1956, 578.

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groups, have widely differing mobility; *epi*quercitol has a much higher mobility in the dilute buffer than *neo*- or *allo*-inositol which contain a larger number of *cis*-1 : 2-diol groups. *scyllo*Quercitol and 2-*O*-methyl*myo*inositol migrate, the latter to a very considerable extent, although each of their adjacent hydroxyl groups is *trans*-situated to one another. It appears, therefore, that a structural feature other than the presence of *cis*-glycol groups is involved in complex formation and that the correct structure would not necessarily be derived from the postulate of a direct relation between M_G value and

TABLE 1. *Ionophoretic mobilities, equilibrium constants of borate complex formation, and rates of oxidation by periodic acid, of cyclitols and related compounds.*

	M_G values in 0·15M-sodium tetraborate soln.	0·012M-	0·05M- *	K † at 22°	$T_{\frac{1}{2}}$ (min.) ‡ at 21°
Inositols					
scyllo- (1 : 3 : 5/2 : 4 : 6)	Not located	0·02	0·05	—	178
(+)-(1 : 2 : 4/3 : 5 : 6)	0·83	0·28	0·69	—	19
neo- (1 : 2 : 3/4 : 5 : 6)	0·77	0·30	—	—	22
myo- (1 : 2 : 3 : 5/4 : 6)	0·60	0·30	0·53	25	80
muco- (1 : 2 : 4 : 5/3 : 6)	0·97	0·87	0·96	—	31
allo- (1 : 2 : 3 : 4/5 : 6)	0·96	0·54	0·88	—	1·5
epi- (1 : 2 : 3 : 4 : 5/6)	0·74	1·50	0·73	$7·0 \times 10^3$	0·9
cis- (all-*cis*)	0·73	1·60	—	$1·1 \times 10^6$	0·9
Quercitols					
scyllo- (1 : 3 : 5/4 : 6)	0·23	0·05	—	5·0	100
proto- (1 : 3 : 4/2 : 5)	0·31	0·05	—	—	34
vibo- (1 : 2 : 4/3 : 5)	0·31	0·07	—	—	48
epi- (1 : 2 : 3 : 5/4)	0·78	1·17	—	$3·1 \times 10^2$	25
cis- (all-*cis*)	0·80	1·60	—	$7·9 \times 10^3$	1·2
Inositol Me ethers					
1-Me-*myo*- (bornesitol)	0·15	0·02	0·12	—	156
2-Me-*myo*-	0·63	0·29	—	—	162
4-Me-*myo*- (ononitol)	0·60	0·45	—	—	100
5-Me-*myo*- (sequoyitol)	0·24	0·05	0·18	—	73
1-Me-(−)-	0·32	—	—	—	—
2-Me-(−)- (quebrachitol)	0·29	0·14	0·31	—	86
3-Me-(+)- (pinitol)	0·73	0·23	0·66	—	28
1 : 3-diMe-*myo*- (dambonitol)	0·00	0·00	—	—	660
	(by definition)				
***cyclo*Hexanetriols**					
1 : 3/2	0·00	0·00	—	—	—
1 : 2/3	0·20	0·08	0·10	—	—
cis-1 : 2 : 3	0·07	0·05	0·19	—	—
cis-1 : 3 : 5 (phloroglucitol)	Not located	0·11	—	32	—
***cyclo*Hexanediols**					
trans-1 : 2	0·00	0·00	—	—	—
cis-1 : 2	0·11	0·01	—	—	—
trans-1 : 3	0·00	0·00	—	—	—
cis-1 : 3	0·01	0·00	—	—	—

* Foster's values.[6a] Foster refers [4, 5] to "0·2M-sodium borate at pH 10," a description which does not define the composition of his electrolyte. From an earlier paper [3] it appears that he used a buffer made from 6 parts of a solution 0·2M in boric acid and 0·1N in sodium hydroxide, and 4 parts of 0·1N-sodium hydroxide. This buffer (which is not 0·2M in borate) is equivalent in borate concentration to 0·05M-sodium tetraborate (19·07 g. of $Na_2B_4O_7,10H_2O$ per l.).

† $K = [\text{complex}^-]/[\text{borate}^-][\text{cyclitol}]$.

‡ $T_{\frac{1}{2}}$ is the time required for the consumption of 0·5 mol. of periodic acid under the conditions given in the Experimental Part.

the number of *cis*-1 : 2-hydroxyl groups. It is true, however, that all *cyclo*hexane derivatives which contain *cis*-1 : 2-diol groups show ionophoretic mobility, at least in the more concentrated electrolyte solution. It is seen also from Table 1 that additional *trans*-hydroxyl groups increase the M_G values, probably by an inductive effect on complex formation.

Another anomaly was noted in the ionophoresis of the *cyclo*hexane-1 : 2 : 3-triols;

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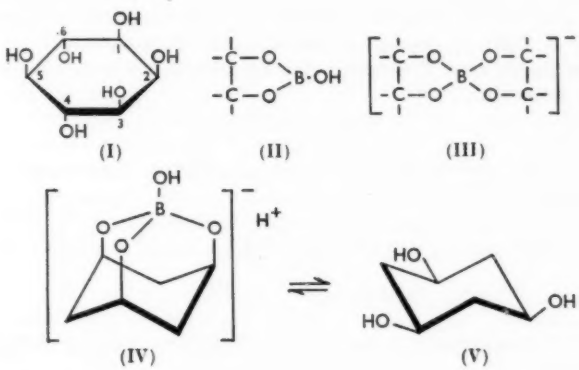
contrary to Foster's statement,[6b] the 1 : 2/3-isomer has a higher mobility than the *cis*-1 : 2 : 3-compound. The identities of the isomers,[10] which were kindly given to us by Professor Th. Posternak, were carefully checked and the ionophoresis carried out repeatedly, leaving no doubt that the isomer with only two *cis*-hydroxyl groups had a higher M_G value than the one with three.

There are four cyclitols (*cis*- and *epi*-inositol, *cis*- and *epi*-quercitol) which have higher M_G values in the dilute than in the more concentrated borate solution. This increase is caused by two factors: (*a*) by a decrease in the mobility of glucose on dilution of the electrolyte (from an average of 14·5 cm. in 0·15M- to 11·7 cm. in 0·012M-sodium tetraborate solution in 4 hours at 11 v/cm.), since the M_G values are relative to the movement of glucose; and (*b*) by an actual increase in the migration distance of these cyclitols on dilution. The rate of migration depends on the extent of complex formation and also on the ionic mobility of the complex; since the extent of complex formation cannot increase on dilution, the greater rate of migration can only be due to higher mobility of the complex anion, there being less interference by other ions in the solution.

According to the extensive studies of Böeseken and his school,[8] 1 : 2-glycols form two different types of chelate compounds with boric acid: simple esters (II) in a 1 : 1 ratio and complexes containing a *spiro*-boron atom (III) in a 2 : 1 ratio. The former [11] are acids comparable in strength to boric acid whereas the latter are strong acids, extensively ionised; it is not known whether they can exist in the undissociated form. Complexes of type (III) cause the increased acidity and conductivity of boric acid solutions after the addition of glycols. It is not known whether complex (II) or (III), or both, are responsible for the ionophoresis of glycols.



(I) (II) (III)

(IV) (V)

The four fast-moving cyclitols have one feature in common: the presence of three *cis*-oriented 1 : 3 : 5-hydroxyl groups. It appears therefore that in these cases complex formation with boric acid occurs by a reaction different from those discussed previously, namely, by a three-point attachment as in (IV): these complexes will be referred to as "tridentate complexes" in contrast to the "Böeseken complexes" formed by *cis*-1 : 2-glycols.[8] On formation of the tridentate complex, the more stable chair form (V) (the one containing the larger number of equatorial hydroxyl groups) must be inverted to the less stable chair form which has the 1 : 3 : 5-hydroxyl groups in axial positions—except in the case of *cis*inositol where both chair forms contain 1a : 3a : 5a-hydroxyl groups.

The data in Table 1 give much support to this hypothesis. The migration of *scyllo*-quercitol, which cannot form a Böeseken complex, is explained by tridentate borate

[10] Posternak and Ravenna, *Helv. Chim. Acta*, 1947, **30**, 441.
[11] Hermans, *Z. anorg. Chem.*, 1925, **142**, 83.

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formation. *cis*-Phloroglucitol (V) should also form such a complex and it was indeed found to migrate even in the dilute borate solution (it could not be revealed by our spray reagents in the stronger electrolyte). The behaviour of the *O*-methyl*myo*inositols is highly significant: blocking of the 2- or 4-hydroxyl group has no effect on ionophoretic mobility, although the former destroys the possibility of formation of Böeseken complexes; methylation in the 1- or the 5-position reduces the M_G value considerably although the latter leaves all the contiguous *cis*-hydroxyl groups intact. The low M_G value of the 5-methyl ether (sequoyitol), in fact, indicates the extent to which Böeseken complexes can contribute to the mobility of *myo*inositol.

Tridentate complexes (IV) are formed in a ratio of 1 : 1 from their components and would be expected to be strong acids. Boric acid itself is a weak Lewis acid with little tendency to form the tetrahedral borate ion,[12] $B(OH)_4^-$, because its planar form is considerably stabilised by resonance involving the limiting structures $H^+O{=}B^-(OH)_2$. Brown and Fletcher[13] found it impossible to prepare a compound containing tervalent tetrahedral boron; forcing boric acid out of planarity, as in complex (IV), destroys the resonance and makes it a strong Lewis acid. Tridentate complexes can therefore be distinguished from those of type (II) and (III) by showing that they contain their components in a 1 : 1 ratio and are strongly acidic. It was found that all the cyclitols which show ionophoretic mobility depress the pH of a borate solution; in solutions which were 0·0025M in sodium tetraborate (pH 9·22) and 0·02M in cyclitol the following pH values were found: *scyllo*- 9·20, *myo*- 9·09, (—)- 8·99, *allo*- 8·88, *muco*- 8·85, *epi*- 7·18, and *cis*-inositol 5·04; *scyllo*- 9·21, *epi*- 8·49, and *cis*-quercitol 7·15; quebrachitol 9·17; *cis*-phloroglucitol 9·10; mannitol 7·57.

It was possible to calculate K, the equilibrium constant of complex formation, from the pH changes and to show that the complexes are produced from boric acid and cyclitols containing *cis*-1 : 3 : 5-triol groupings in equimolecular proportions.

Calculation of Equilibrium Constants.—The equilibrium constant of the formation of a 1 : 1 complex is defined as

$$K = [C^-]/[B^-][Cy] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $[C^-]$, $[B^-]$, and [Cy] are the concentrations of the complex anion, borate ion, and cyclitol, respectively.*

If one litre of solution is made up from sodium hydroxide, a moles of boric acid, and na moles of cyclitol, then the total concentration of boric acid in various forms is

$$a = [HB] + [B^-] + [HC] + [C^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where [HB] is the concentration of boric acid and [HC] that of the conjugate acid of the complex anion, and

$$na = [Cy] + [HC] + [C^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Since the molarity of anions and cations must be equal, it follows that:

$$[C^-] + [B^-] + [OH^-] = [Na^+] + [H^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Substitution of the value of $[C^-]$ from equation (4) and of the dissociation constants of

* This definition of K does not imply that the complex is formed by the reaction of borate ions with the cyclitol. It is much more likely that the cyclitol reacts with boric acid, but this is not relevant to our discussion. An equilibrium constant defined as $K' = [C^-][H^+]/[HB][Cy]$ would involve inconveniently small quantities in the calculations and would only differ by a constant from K, since it can be shown that $K' = KK_{aB}$. As defined in (1), the value of K allows immediate calculation of the extent of complex-formation in a borate solution of known concentration.

[12] Edwards, Morrison, Ross, and Schultz, *J. Amer. Chem. Soc.*, 1955, **77**, 266.
[13] Brown and Fletcher, *ibid.*, 1951, **73**, 2808.

boric acid and of the complex, $K_{aB} = [B^-][H^+]/[HB]$ and $K_{aC} = [C^-][H^+]/[HC]$, into equation (2) gives:

$$[B^-] = \frac{a - \{[Na^+] + [H^+] - [OH^-]\}\{1 + [H^+]/K_{aC}\}}{[H^+]/K_{aB} - [H^+]/K_{aC}} \quad . \quad . \quad . \quad (5)$$

From equation (4), we have

$$[C^-] = [Na^+] + [H^+] - [OH^-] - [B^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

and from equation (3)

$$[Cy] = na - [C^-]\{1 + [H^+]/K_{aC}\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

In our experiments, excess of cyclitol ($n > 1$) was added to 0·0025M-sodium tetraborate and the pH measured. In our case, therefore, $a = 0{\cdot}01$ and $[Na^+] = 0{\cdot}005$; K_{aB} is known to be 6×10^{-10}; K_{aC} is not known but, the complex being a fairly strong acid, $[H^+]/K_{aC}$ was neglected at low hydrogen-ion concentrations. From the measured pH values, $[B^-]$, $[C^-]$, and [Cy] were calculated by equations (5), (6), and (7) and substituted into equation (1): for those cyclitols where tridentate complexing was postulated, K proved constant over a wide range of cyclitol concentration, showing that the complexes are formed in a 1 : 1 ratio.

The K values are listed in Table 1, and, as examples, the calculation of K for *epi*- and *myo*inositol is given in Table 2.

*cis*Inositol, which forms the most stable complexes, and therefore lowers the pH of borate solutions to the largest extent, does not give constant K values by the above method of calculation. This indicates that at the low pH values (below 5) produced here, the $[H^+]/K_{aC}$ term in equations (5) and (7) can no longer be neglected. Use of the value of $1{\cdot}8 \times 10^{-4}$ for K_{aC} gives constant K values as shown in Table 2. The calculations show that below pH 5 undissociated complex acid is present in considerable amounts, and give the value of its acid dissociation constant. The structure of this complex acid is uncertain; in view of Brown and Fletcher's results [13] it is unlikely to contain a tervalent boron atom and would probably be hydrated, corresponding to the addition of a proton to (and not to the removal of OH^- from) the complex anion (IV). It is intended to attempt the isolation of tridentate cyclitol complexes later.

TABLE 2. *Calculation of equilibrium constants.*

	*epi*Inositol		*myo*Inositol		*cis*Inositol			(−)-Inositol
						10^4K		
n	pH	10^3K	pH	K	pH	*	†	pH
2	7·18	7·25	9·09	19	5·04	1·0	1·08	8·99
4	6·84	6·95	8·94	24·6	4·70	0·95	1·08	8·89
8	6·50	7·0	8·75	25·6	4·42	0·84	1·10	8·61
12	6·32	6·95	8·63	25·0	4·29	0·74	1·07	8·38
16	6·20	6·8	8·52	25·6	4·20	0·68	1·09	8·20
20	—	—	—	—	4·14	0·62	1·09	—
32	—	—	8·24	27·3	—	—	—	7·76
Average		7·0 (± 0·2)		25·5 (± 1)			1·09	

* Calculated neglecting $[H^+]/K_{aC}$. † Calculated using the value of $1{\cdot}8 \times 10^{-4}$ for K_{aC}.

Cyclitols not possessing *cis*-1 : 3 : 5-triol groupings do not give constant K values by equation (1). Mannitol–borate complexes, according to Antikainen,[14] obey the $K = [C^-]/[B^-][\text{mannitol}]^{1{\cdot}8}$ equation, indicating the presence of both 1 : 1 and 2 : 1 complexes. We have found that (−)-inositol and quebrachitol follow approximately the $K = [C^-]/[B^-][Cy]^{1{\cdot}5}$ equation; the pH variation of the former is shown in Table 2.

[14] Antikainen, *Acta Chem. Scand.*, 1955, **9**, 1008.

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The equilibrium constants are in the expected order. *cis*Inositol, with three axial hydroxyl groups on the same side of the ring in either chair form, forms by far the firmest complex. *epi*Inositol and *cis*-quercitol also form firmer complexes than mannitol. *scyllo*Quercitol and *myo*inositol have two axial hydroxyl groups on the same side in the tridentate complexes which increase their free energy and therefore reduce their equilibrium constants. Böeseken and Julius [15] found no complex-formation between *myo*-inositol and boric acid; this is not surprising since calculation, using the value of $K = 25$, shows that in 0·5M-boric acid containing an equimolecular amount of *myo*inositol, complex is formed to an extent of 0·02% only. The configuration of *scyllo*inositol is most unfavourable for tridentate complex formation since it would result in the interaction of three axial hydroxyl groups; tridentate complex formation with two molecules of boric acid would be possible but does not seem to occur. The K values have been used for the calculation of the various repulsive interactions in cyclitol molecules.[16]

Tridentate-complex formation, therefore, explains the anomalies of ionophoresis in borate buffers. The extent of complex-formation, calculated from equation (1) with the use of the K values in Table 1, closely parallels the M_G values. *cis*Quercitol and *cis*- and *epi*inositol exist practically 100% as complex, even in the more dilute electrolyte; glucose so exists to a smaller extent. In the 0·15M-buffer, several cyclitols show greater mobility than the most highly complexed *cis*inositol, which probably indicates that they have, to some extent, combined with a second molecule of boric acid and thereby acquired a double charge; they all possess two pairs of *cis*-1 : 2-diol groups.

Tridentate complexes with borate have not been reported before. It is reasonable to expect that they will be found with compounds other than cyclitols: the ionophoretic migration of pentaerythritol [9] is probably explained by it, and Foster and Stacey's results [5] with glucofuranosides strongly suggest formation of tridentate complexes with the oxygen atoms at $C_{(3)}$, $C_{(5)}$, and $C_{(6)}$.

The Rate of Periodate Oxidations.—For comparison with borate complex formation, the study was extended to another reaction which depends on the relative configuration of hydroxyl groups: oxidative fission by periodic acid. It is believed [17,18] that in this reaction a cyclic intermediate is formed which —like the borate ester or the *iso*propylidene compounds—contains a five-membered ring; but the large iodine atom (I–O distance is 1·93 Å) can bridge the oxygen atoms of *trans-cyclo*hexane-1 : 2-diols whereas boric acid (B–O = 1·38 Å) or acetone (C–O = 1·44 Å) usually reacts with *cis*-glycols only.[19] In the *cyclo*hexane system *cis*-glycols are oxidised more rapidly by periodic acid than their *trans*-isomers; [17] isolated examples of this phenomenon are found in cyclitol chemistry. Thus, Posternak [20] observed that *myo*inositol consumed periodic acid faster than *scyllo*-inositol, and similar measurements have been used to assign configurations to some inosamines.[21] The three *cyclo*hexane-1 : 2 : 3-triols behave similarly,[10] the all-*cis*-isomer being oxidised the fastest and the all-*trans*-isomer the slowest. The fission of the *cyclo*-hexane-1 : 2 : 3 : 4-tetrols has also been investigated.[22] Fleury, Courtois, and Bieder [23] have compared the rates of the reaction of several cyclitols.

Inositols and quercitols consume six mols. of periodic acid by a mechanism which is still under discussion.[24] Obviously, only the rate of the first step, the opening of the ring, will depend on the *cis*- or *trans*-relation of the hydroxyl groups; after the initial ring-fission all the isomers will react at similar rates. Fleury *et al.*[23] measured the consumption

[15] Böeseken and Julius, *Rec. Trav. chim.*, 1926, **45**, 489.
[16] Angyal and McHugh, *Chem. and Ind.*, 1956, 1147.
[17] Price and Knell, *J. Amer. Chem. Soc.*, 1942, **64**, 552.
[18] Buist and Bunton, *J.*, 1955, 1406.
[19] Angyal and Macdonald, *J.*, 1952, 686.
[20] Posternak, *Helv. Chim. Acta*, 1944, **27**, 466.
[21] *Idem, ibid.*, 1950, **33**, 1597.
[22] Posternak and Friedli, *ibid.*, 1953, **36**, 259.
[23] Fleury, Courtois, and Bieder, *Bull. Soc. chim. France*, 1953, 543.
[24] Schwarz, *Chem. and Ind.*, 1955, 1388; Fleury and Le Dizet, *Bull. Soc. Chim. biol.*, 1955, **37**, 1099.

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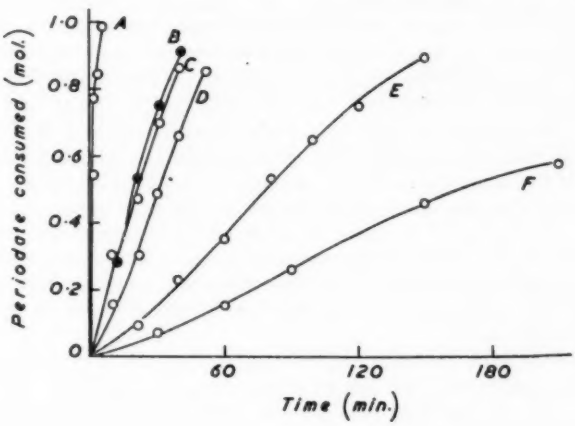
of periodic acid for all compounds *after the same time*, thereby observing them at different stages of the oxidation.

We have determined the initial rate of the periodic acid oxidation by carrying out the reaction at such dilution that several titrations could be performed before one mol. of the oxidant was consumed. Plots of periodic acid consumption *versus* time were drawn and by interpolation the time required for the uptake of 0·5 mol. of periodic acid, $T_{\frac{1}{2}}$, was determined. Several examples of these plots are shown in the Figure, and the $T_{\frac{1}{2}}$ values are listed in the last column of Table 1.

The initial rates show a surprisingly wide range. Whereas Posternak found [20] that *myo*inositol was oxidised about twice as fast as the *scyllo*-isomer, it is now seen that the *cis*-compound reacts about 200 times faster. The reaction of *epi*- and *cis*-inositol is so rapid that only approximate $T_{\frac{1}{2}}$ values could be determined; on the other hand, dambonitol reacts so slowly that the 0·5 mol. consumption of oxidant was not reached and was determined by extrapolation.

The shape of the plots of some slowly reacting cyclitols (initial increase in velocity, see Figure) indicates that the initial ring-fission is accompanied by the—apparently



faster—subsequent oxidations, and the measured rate is higher than that of the initial fission. For this reason no attempt was made to calculate rate constants. The difference between the rapidly- and the slowly-reacting cyclitols is therefore even greater than shown by the figures.

The reciprocal of $T_{\frac{1}{2}}$ is an additive quantity and can be used for calculations. For example, from the $10^3/T_{\frac{1}{2}}$ value of *scyllo*inositol (5·6) it follows that the value for *one trans*-hydroxyl pair is 0·9; by using this value and 12·5 for *myo*inositol (in which there are four *trans*- and two *cis*-pairs), the $10^3/T_{\frac{1}{2}}$ value for *one cis*-hydroxyl pair in *myo*-inositol is found to be 4·4. With these values for each *cis*- and *trans*-pair, the following $10^3/T_{\frac{1}{2}}$ values have been calculated for the methyl ethers of *myo*inositol (with the experimentally determined values in parentheses): 1-Me 7·1 (6·4), 2-Me 3·6 (6·2), 4-Me 10·6 (10·0), 5-Me 10·6 (13·7), 1 : 3-Me_2 1·8 (1·5). The agreement is reasonable if it is taken into account that the 2-methyl ether, with its methoxy-group in axial position, has a higher energy than its isomers, which increases the rate of fission (see below).

The same value (4·4) for a *cis*-hydroxyl pair cannot be used for any other cyclitol. Each pair in, for example, (−)-inositol is oxidised considerably faster than in *myo*inositol. It is necessary to point out that the three contiguous *cis*-hydroxyl groups in the latter present a rather unfavourable conformation for the attachment of a five-membered ring

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(borate, *iso*propylidene compound, or cyclic periodate); the necessary movement [19] of the central (axial) hydroxyl group towards coplanarity with another hydroxyl group is impeded by the two bulky equatorial neighbours (VI). When the axial hydroxyl group

(VI) (VII)

is flanked by another axial group [as in (−)-inositol or *proto*quercitol] or only by hydrogen atoms (as in *vibo*quercitol), the deformation required for the attachment of the five-membered ring is more readily achieved. This is also seen in borate-complex formation and explains the behaviour of the *cyclo*hexane-1 : 2 : 3-triols referred to above: the all-*cis*-isomer contains the unfavourable arrangement of the three *cis*-hydroxyl groups. Posternak and Ravenna's data,[10] show that although the all-*cis*-isomer is oxidised faster by periodic acid than the 1 : 2/3-triol, it is not oxidised *twice* as fast, as it should if other conditions were equal. The exceptionally slow reaction of *myo*inositol with acetone to form an *iso*propylidene derivative [25] is another example of this effect.

Four of the cyclitols react very much faster with periodic acid than the others, and all the four contain two axial hydroxyl groups on the same side of the ring, an arrangement introducing extra energy (estimated [16] at 2·8 kcal./mole). Buist and Bunton [18] have shown that in the reaction of ethylene glycol with periodic acid the cyclic complex is formed by a fast reversible reaction, and subsequently breaks down with carbon–carbon bond fission. If the same mechanism is assumed to apply to cyclitols, the rate and the position of the equilibrium of complex formation will depend strongly on the relative position of the two hydroxyl groups. The rate of the fission of the complex, however, may well depend on the strain in the molecule, greater interaction energy lowering the activation energy of this reaction. It is suggested that the interaction of axial hydroxyl groups provides the explanation for the fast rate of glycol fission in *cis*-, *epi*-, and *allo*-inositol and in *cis*quercitol.

The behaviour of *muco*inositol is not fully understood: it is the only cyclitol with two axial hydroxyl groups on the same side which is not rapidly oxidised. Barton [26] has shown that, in many cases, 1 : 3-diaxial substitution renders an axial substituent at $C_{(2)}$ more stable than an equatorial one. *muco*Inositol (VII) has this configuration and may therefore have a lower free energy than the other diaxially substituted cyclitols. (γ-Benzene hexachloride, which has the *muco*-configuration, is the only 1 : 3-diaxially substituted isomer readily formed in the chlorination of benzene.)

Experimental

Materials.—*muco*Inositol was kindly given to us by Dr. Laurens Anderson (Madison), the *cyclo*hexanetriols by Professor Th. Posternak (Geneva), and the *cyclo*hexane-1 : 3-diols by Dr. W. Rigby (Birkbeck College). *allo*Inositol was synthesised by P. T. Gilham (method to be published). The other compounds were prepared or obtained as described in previous papers.[19, 25, 27, 28]

Paper Ionophoresis.—The apparatus and the method used were essentially those described by Foster.[29] The two glass plates were 18″ long and the filter paper (Whatman No. 1), cut to a size of 5 in. × 22 in., dipped about one inch below the surface of the sodium tetraborate solution

[25] Angyal, Gilham, and Macdonald, preceding paper.
[26] Barton, *Chem. and Ind.*, 1953, 664.
[27] Angyal and Matheson, *J. Amer. Chem. Soc.*, 1955, **77**, 4343.
[28] Angyal and McHugh, *Chem. and Ind.*, 1955, 947.
[29] Foster, *ibid.*, 1952, 1050.

in each container. A potential of 550 v was applied, giving a current of 16—17 and 2 milliamp. with 0·15M- and 0·012M-sodium tetraborate, respectively. The rise in temperature was negligible, making cooling unnecessary.

Unfortunately sodium borate interferes with the detection of the cyclitols by the usual reagents,[7] particularly by silver nitrate, and consequently larger amounts are required than in paper chromatography. In our experience Lemieux and Bauer's permanganate–periodate reagent[30] gives the best results. Whilst paper ionophoresis is useful for the identification of cyclitols, it is not particularly suitable for the detection of minor components in a mixture. The difficulties of detection may be obviated in the future by the use of glass filter-paper.[31]

The ionophoretic mobilities are expressed[4] as M_G values, that is, the ratio of the true distance of migration of the substance to that of glucose. The true distances are those corrected for electroendosmotic flow by reference to a non-complexing compound. Foster used 2 : 3 : 4 : 6-tetra-*O*-methylglucose as the reference compound; this is not detected by the Lemieux–Bauer spray and so dambonitol, shown to have the same movement as tetra-*O*-methylglucose (silver nitrate spray) was substituted. It was later found that dambonitol was not an ideal substance for this purpose since its movement with the electroendosmotic flow was somewhat dependent on its concentration and it had to be applied in high concentration to be detected. The outer edge of the dambonitol spot indicates the correct position for the M_G value of 0; a correction has been applied accordingly where necessary. *trans-cyclo*Hexane-1 : 2- or -1 : 3-diol would be better non-migrating markers.

Approx. 40 μg. of a cyclitol were applied to the paper; the non-migrating diols and triols required 200, dambonitol 800, and *cis*-phloroglucitol about 1200 μg. After spraying with the Lemieux–Bauer reagent, the paper was placed between two glass plates to prevent evaporation; the spots appeared after ½—1½ hr., depending on the nature and the concentration of the compound. Surprisingly, *scyllo*inositol was not revealed by this, or any other, reagent in any concentration on paper saturated with 0·15M-borate. The extensive diffusion of *myo*inositol, described by Foster,[6b] was never observed but glucose streaked strongly in 0·012M-borate buffer: its highest concentration (that is, the first appearance of a yellow spot) was taken as its true position.

The M_G values given in Table 1 are the averages of several determinations.

Determination of Equilibrium Constants.—The pH-meter (Cambridge Portable pH Meter) was adjusted with 0·0025M-sodium tetraborate to pH 9·22, the value calculated from the acid dissociation constant of boric acid; this procedure permitted the use of equations (5) to (7) without any correction. The cyclitols were added as solids to the borate solution and the pH was read after each addition.

Rate of Periodic Acid Oxidations.—Periodate solution (1 ml. containing approx. 2·5 mg. of $NaIO_4$) was rapidly added to a mixture of N-sulphuric acid (1 ml.), cyclitol solution (1 ml. containing 1·0 mg. of cyclitol), and water (20 ml.). The time was estimated from the moment the last amount of periodate solution left the pipette. After a suitable time the mixture was treated with N-sodium hydroxide (0·5 ml.), 20% aqueous sodium acetate (1·5 ml.), and a few crystals of potassium iodide. The liberated iodine was immediately titrated with 0·01N-sodium thiosulphate, four drops of 5% starch solution (in formamide) being added near the end-point. A blank determination gave the initial concentration of periodic acid. The titrations were made at appropriate intervals, depending on the rate of oxidation of the cyclitol being measured.

The authors are grateful to Dr. J. A. Mills (Adelaide) for helpful discussions.

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[30] Lemieux and Bauer, *Anal. Chem.*, 1954, **26**, 920.
[31] Briggs, Garner, and Smith, *Nature*, 1956, **178**, 154.

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269. *The Paper Chromatography of Cyclitols.*

By S. J. Angyal, D. J. McHugh, and P. T. Gilham.

Cyclitols are particularly suitable for paper chromatography: they are in most cases easily separated and readily detected, and the separations can be translated to a preparative scale by the use of cellulose-powder chromatography. R_F values for several inositols in aqueous acetone were reported [1] and recently Posternak [2] gave values for many cyclitols and related compounds in several solvent systems. In the Table we now list R_F values for all the inositols and for the known quercitols and inositol methyl ethers. Aqueous acetone is the solvent of choice in most cases because by its use chromatograms can be run, dried, and developed within 3—4 hr. In the authors' laboratory chromatograms are now run as a routine matter in aqueous acetone before the working-up of reaction mixtures.

The best method for detecting cyclitols on paper is the silver nitrate–sodium hydroxide reagent described by Trevelyan *et al.*,[3] as modified by Anet and Reynolds; [4] fixation by thiosulphate gives black spots which can be preserved as a permanent record. The older ammoniacal silver nitrate reagent [1] is less sensitive and usually causes darkening of the whole paper. The sensitivity of the reagent decreases with decreasing number of hydroxyl groups; while 10 μg. of an inositol is readily detected, about 50 μg. of a monomethyl inositol and 500 μg.

R_F values of cyclitols.

Solvents: *A*, acetone–water (4 : 1, v/v); *B*, phenol–water (4 : 1, w/w); *C*, butanol–acetic acid–water (4 : 1 : 1); *D*, ethanol–water–conc. ammonia solution (20 : 4 : 1).

Solvent	*A*	*B*	*C*	*D*
D-Glucose	0·43	0·35	0·175	0·64
Inositols				
scyllo- (1 : 3 : 5/2 : 4 : 6)	0·17	0·155	0·07	0·40
(+)- (1 : 2 : 4/3 : 5 : 6)	0·27	0·195	0·10	0·50
neo- (1 : 2 : 3/4 : 5 : 6)	0·19	0·24	0·085	0·42
myo- (1 : 2 : 3 : 5/4 : 6)	0·185	0·205	0·08	0·41
muco- (1 : 2 : 4 : 5/3 : 6)	0·35	0·265	0·145	—
allo- (1 : 2 : 3 : 4/5 : 6)	0·30	0·29	0·135	—
epi- (1 : 2 : 3 : 4 : 5/6)	0·22	0·33	0·105	0·46
cis- (all-*cis*)	0·22	0·35	0·125	—
Quercitols				
scyllo- (1 : 3 : 5/4 : 6)	0·31	0·37	0·145	0·63
proto- (1 : 4/2 : 3 : 5)	0·405	0·38	0·20	0·67
vibo- (1 : 2 : 4/3 : 5)	0·33	0·42	0·155	0·63
epi- (1 : 2 : 3 : 5/4)	0·34	0·41	0·16	—
cis- (all-*cis*)	0·39	0·54	0·205	—
Inositol methyl ethers				
1-Me-*myo*- (bornesitol)	0·30	0·50	0·15	0·58
2-Me-*myo*-	0·35	0·50	0·16	0·61
4-Me-*myo*- (ononitol)	0·33	0·50	0·16	—
5-Me-*myo*- (sequoyitol)	0·33	0·47	0·165	0·58
1-Me-(−)	0·43	0·49	0·19	0·64
2-Me-(−) (quebrachitol)	0·39	0·46	0·185	0·64
3-Me-(+) (pinitol)	0·44	0·45	0·20	0·64
1 : 3-diMe-*myo*- (dambonitol)	0·50	0·69	0·27	0·69

of dambonitol are required to cause a similar spot: heating the paper for a short time increases the sensitivity to methyl ethers. For dambonitol, Lemieux and Bauer's permanganate–periodate reagent [5] is more suitable; it is a good reagent for all cyclitols and its sensitivity does

[1] Ballou and Anderson, *J. Amer. Chem. Soc.*, 1953, **75**, 648.
[2] Posternak, Reymond, and Haerdi, *Helv. Chim. Acta*, 1955, **38**, 1911.
[3] Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444.
[4] Anet and Reynolds, *ibid.*, 1954, **174**, 930.
[5] Lemieux and Bauer, *Analyt. Chem.*, 1954, **26**, 920.

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not vary much with the number of hydroxyl groups, but the spots are not permanent. The Scherer reagent [6] is specific for inositols only but lacks sensitivity. In some cases Hockenhull's [7] borate–phenol-red reagent is useful because it is more sensitive to those cyclitols which form complexes readily with borate,[8] *e.g.*, small amounts of *cis*inositol can be detected in the presence of *myo*inositol. It is also useful when the cyclitols are to be preserved, for example, for elution; all the other reagents referred to destroy the compounds.

For the separation of *cis*- and *epi*-inositol ethyl acetate–acetic acid–water (3 : 1 : 1; v/v) is useful, the R_F values being: *myo*- 0·15, (±)- 0·20, *epi*- 0·20, and *cis*-inositol 0·25.

The R_F values were determined on descending chromatograms (although the ascending technique is used for routine testing). With butanol–acetic acid–water, the chromatograms were run for 24 hr., the solvent dripping off the serrated end of the paper to give relative R_F values; absolute values were calculated by comparison with a chromatogram of a few substances (of higher R_F values) for which the solvent was run only to the end of the paper. Whatman No. 1 paper was used throughout. Papers wetted with phenol or butanol were dried overnight but those with acetone require only a few minutes' drying. The R_F values vary considerably, unless stringent precautions are taken to assure constant conditions, but their ratio to the R_F value of glucose (the R_G value) is easily reproducible; glucose was therefore incorporated in all chromatograms and its R_F values are given in the Table.

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[6] Fleury, Courtois, and Malangeau, *Bull. Soc. Chim. biol.*, 1953, **35**, 537.
[7] Hockenhull, *Nature*, 1953, **171**, 982.
[8] Angyal and McHugh, preceding paper.

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270. *Conversion of Methyltrichlorosilane into Chloromethyl Derivatives of Silane.*

By H. D. Kaesz and F. G. A. Stone.

Silicon compounds containing chloromethyl groups have been widely studied; [1] however, few chloromethyl derivatives of silane with silicon–hydrogen bonds are known. Only $CH_2Cl{\cdot}SiHMe_2$ and $CH_2Cl{\cdot}SiHEt_2$ are well characterised,[2] although chloromethylsilane, $CH_2Cl{\cdot}SiH_3$, has been reported,[3] having been obtained in poor yield by refluxing chloromethyltrichlorosilane with lithium hydride in di*iso*pentyl ether for two days. A convenient general method for preparing chloromethyl derivatives of silane, *e.g.*, $CHCl_2{\cdot}SiH_3$, by reducing chloromethylchlorosilanes with lithium aluminium hydride, is now described. Reaction occurs rapidly at 0°. Diethyl or dibutyl ether may be used as solvent, the choice depending on the boiling point of the product. The chloromethylsilane produced was recovered by distillation *in vacuo* at or below room temperature and purified by fractional distillation at atmospheric pressure. In this way chloromethylsilanes were quickly isolated from metal halides, in the presence of which they exchanged hydrogen on silicon for chlorine. Chloromethylsilane, $CH_2Cl{\cdot}SiH_3$, was obtained in nearly 80% yield, and dichloromethylsilane, $CHCl_2{\cdot}SiH_3$, and chloromethyldimethylsilane, $CH_2Cl{\cdot}SiHMe_2$, in nearly 90% yield. During reduction of $CHCl_2{\cdot}SiCl_3$ and of $CCl_3{\cdot}SiCl_3$ some difficulty was caused by production of silane as a by-product, perhaps through cleavage of carbon–silicon bonds by lithium aluminium hydride. Indeed, attempts to make $CCl_3{\cdot}SiH_3$ were abandoned owing to the large amounts of silane formed from $CCl_3{\cdot}SiCl_3$ and more particularly owing to explosions that occurred during distillation of $CCl_3{\cdot}SiH_3$ in dibutyl ether. Thus the thermal stability of the chloromethylsilyl compounds apparently decreases in the order $CH_2Cl{\cdot}SiH_3$, $CHCl_2{\cdot}SiH_3$, $CCl_3{\cdot}SiH_3$.

Chloromethylchlorosilanes, from which chloromethylsilanes are prepared, are made principally by photochemical chlorination of methylchlorosilanes. Nevertheless, the

[1] Burkhard, Rochow, Booth, and Hartt, *Chem. Rev.*, 1947, **41**, 97.
[2] Seyferth and Rochow, *J. Amer. Chem. Soc.*, 1955, **77**, 907.
[3] Ponomarenko and Mironov, *Bull. Acad. Sci. U.S.S.R.*, 1954, 423 (*Chem. Abs.*, 1955, **49**, 9495).

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tendency of entering chlorine atoms completely to chlorinate one methyl group in a methylchlorosilane presents a problem as yields of the monochloro-derivatives are lowered, and these are the products usually desired. However, satisfactory yields of *monochlorinated* methylchlorosilanes have been obtained by maintaining the starting material in large excess. With methyltrichlorosilane one such process gave $CH_2Cl{\cdot}SiCl_3$ in 22% yield.[4] In the work described below, the photochemical chlorination technique was improved, and applied to a variety of compounds, giving any required chloromethyl compound in high yield.

Experimental.—Lithium aluminium hydride solutions were analysed immediately before use.[5]

Chloromethylsilane. Chloromethyltrichlorosilane (41·0 g.) was added to dibutyl ether (20 ml.), stirred at 0°, in a flask connected to a high-vacuum apparatus through a trap cooled to −78° and another at −196°. Then 574 ml. of a 1·164N-dibutyl ether solution of lithium aluminium hydride were added dropwise. The reaction vessel and traps which had previously contained purified nitrogen were then evacuated. In this manner liquid product, together with some solvent, was distilled into the trap at −78° while the reaction flask was at 0°. The trap cooled to −196° was intended to collect any silane formed during the reduction, but none was detected. The liquid collected at −78° was fractionally distilled at atmospheric pressure under nitrogen, through a 12″ vacuum-jacketed Vigreux column equipped with a partial-take-off total reflux still-head. At 32° *chloromethylsilane* (13·9 g., 78·5%), n_D^{20} 1·4149 (Found: C, 15·0; H, 6·4; Si, 35·0%; *M*, 81·9. CH_5ClSi requires C, 14·9; H, 6·2; Si, 34·8%; *M*, 81·4) was obtained. Vapour pressures were as tabulated. They correspond to $\log_{10} p(\text{mm.}) = 7{\cdot}593 - 1436/T^{-1}$, an extrapolated b. p. of 31·5° (obs. 32°), a Trouton constant of 21·6 cal. deg.$^{-1}$ mole^{-1}, and a heat of vaporisation 6·572 kcal. mole.$^{-1}$.

Vapour pressure of $CH_2Cl{\cdot}SiH_3$.

Temp.	−27·2°	−21·3°	−18·0°	−5·2°	5·2°	9·8°	19·9°	24·4°
$p_{mm.}$ (obs.)	57·2	78·2	92·6	171·0	271·0	330·1	495·5	589·0
$p_{mm.}$ (calc.)	57·0	78·1	92·5	171·8	272·4	330·4	494·2	586·0

Dichloromethylsilane. 675 ml. of 0·942N-lithium aluminium hydride solution in dibutyl ether, with dichloromethyltrichlorosilane (44·3 g.) in dibutyl ether (25 ml.) at 0°, gave a considerable amount of silane and *dichloromethylsilane* (20·0 g., 86%), b. p. 68°, n_D^{20} 1·4478 (Found: Si, 24·1; Cl, 62·0%; *M*, 116. CH_4Cl_2Si requires Si, 24·4; Cl, 61·6%; *M*, 115). Vapour pressures (tabulated) correspond to $\log_{10} p(\text{mm.}) = 7{\cdot}869 - 1698/T^{-1}$, extrapolated b. p. 67·3° (obs. 68°), Trouton constant 22·8 cal. deg.$^{-1}$ mole^{-1}, and heat of vaporisation 7·771 kcal. mole^{-1}.

Vapour pressure of $CHCl_2{\cdot}SiH_3$.

Temp.	10·4°	15·1°	20·5°	24·8°	29·8°	35·2°	40·2°	45·6°
$p_{mm.}$ (obs.)	76·1	95·2	123·0	149·3	185·1	231·7	282·4	346·4
$p_{mm.}$ (calc.)	76·1	95·1	122·2	148·0	184·2	230·2	282·1	348·4

In attempted preparations of trichloromethylsilane from trichloromethyltrichlorosilane and lithium aluminium hydride at low temperatures much silane was formed. Attempted removal of $CCl_3{\cdot}SiH_3$ from its dibutyl ether solution, by distillation under nitrogen, led to explosions. The b. p. of the presumed derivative $CCl_3{\cdot}SiH_3$ was recorded as 81°/760 mm.

Chloromethyldimethylsilane. 1·430N-Lithium aluminium hydride solution (125 ml.) in diethyl ether was added to $CH_2Cl{\cdot}SiMe_2Cl$ (24·6 g.) in diethyl ether (30 ml.) at 0°. Further treatment was as for the isolation of chloromethylsilane, except that dibutyl ether was added as chaser. Distillation under nitrogen gave chloromethyldimethylsilane (16·1 g., 86%), b. p. 81°, n_D^{20} 1·4178 (lit.,[3] b. p. 80—81°).

Rearrangement of Chloromethylsilanes.—(i) During reduction of freshly distilled chloromethyldimethylchlorosilane, recovery of chloromethyldimethylsilane was attempted by distillation through a column having a Chromel spiral. While $CH_2Cl{\cdot}SiHMe_2$ was being collected at 81°, the temperature at the still-head fell to 57°, and Me_2SiCl (n_D^{20} 1·3890; lit.,[1]

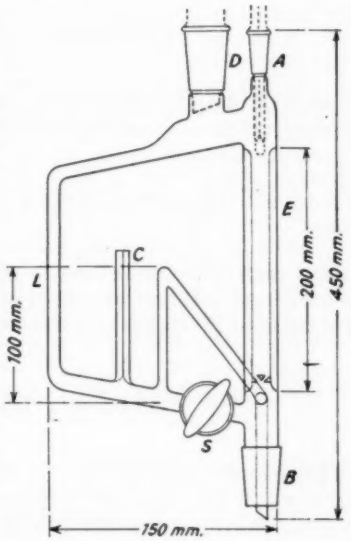
[4] Speier, B.P. 629,719/1949 (*Chem. Abs.*, 1950, **44**, 3518).
[5] Felkin, *Bull. Soc. chim. France*, 1951, 347.

b. p. 57·3°, n_D^{20} 1·3878) in 53% yield was obtained. The final yield of $CH_2Cl{\cdot}SiHMe_2$ was only 36%.

(ii) When $CH_2Cl{\cdot}SiHMe_2$ was distilled through the same column using a glass spiral no rearrangement to Me_3SiCl occurred.

(iii) Chloromethyldimethylsilane decomposed very slowly at room temperature when sealed *in vacuo* in glass containers. In 3 months pure $CH_2Cl{\cdot}SiHMe_2$ suffered about 2% of rearrangement, as found by determination of hydrolysable chlorine.

Chlorination of the Methylchlorosilanes.—The apparatus shown in the Figure was used; essentially only unchlorinated material was in contact with chlorine, and exposed to radiation. Water and solid carbon dioxide condensers were placed at *D*, and a thermometer at *A*. The compound to be chlorinated was heated in a distillation flask at *B*. As soon as liquid collected at *L*, chlorine was admitted through the capillary-tube *C*. Only the tube *L* was irradiated with ultraviolet light. The stopcock *S* was closed, and opened only at the end of reaction. The vacuum-jacketed column *E* packed with glass helices serves to return most higher-boiling chlorinated material to the flask. The temperature of the latter gradually rises to the b. p. of the desired product, whereas the temperature at *A* remains near the b. p. of the starting material, until towards the end of reaction when it rises rapidly. The course of reaction may also be followed by passing the hydrogen chloride gas issuing from the condensers into standard base.



Methyltrichlorosilane was thus chlorinated to give a 46% yield of chloromethyltrichlorosilane, b. p. 117° (Found: C, 6·8; H, 1·3; Si, 15·3; hydrolysable Cl, 58·0. Calc. for CH_2SiCl_4: C, 6·5; H, 1·1; Si, 15·3; hydrolysable Cl, 57·8%) (the b. p. is reported [6] as 116·5°), and a 17% yield of *dichloromethyltrichlorosilane*, b. p. 142°, n_D^{20} 1·4727 (Found: C, 5·7; H, 0·5; Si, 13·2; hydrolysable Cl, 48·9. $CHSiCl_5$ requires C, 5·5; H, 0·5; Si, 12·9; hydrolysable Cl, 48·7%). The constitution of the latter was confirmed by hydrolysis with base: methylene chloride (infrared spectrum identical with that of a pure sample) was obtained rather than a mixture of methyl chloride and chloroform.

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CAMBRIDGE, MASSACHUSETTS. [*Received, September 26th*, 1956.]

[6] Yakubovitch and Ginsburg, *J. Gen. Chem.* (*U.S.S.R.*), 1952, **22**, 1783.

271. *The Preparation of Cyclic Ketones by Use of Trifluoroacetic Anhydride.*

By R. J. FERRIER and J. M. TEDDER.

IT has been shown that trifluoroacetic anhydride will promote condensation of carboxylic acids with activated aromatic compounds to form ketones.[1] This reaction has now been applied to intramolecular condensation of two aromatic acids. γ-Phenylbutyric acid ($n = 3$) has been converted into α-tetralone in good yield in mild conditions, but β-phenylpropionic acid ($n = 2$) gave very poor yields of indan-1-one. Although a better yield of indan-1-one was obtained by using heptafluorobutyric anhydride at a higher temperature the product was contaminated with tar and was hard to purify. As a reagent for promoting this type of ring closure, trifluoroacetic anhydride would appear valuable for the

[1] Bourne, Stacey, Tatlow, and Tedder, *J.*, 1951, 718.

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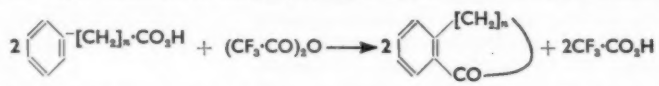
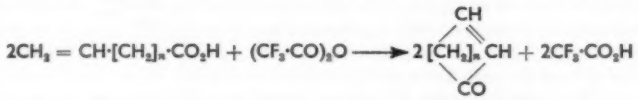
synthesis of six-membered rings ($n = 3$) from compounds too sensitive to be treated with anhydrous hydrogen fluoride or polyphosphoric acid; however it would not appear to be very useful for the synthesis of five-membered rings ($n = 2$).

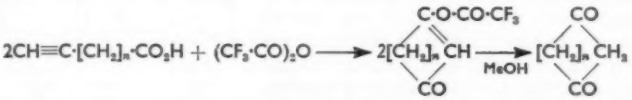
The second reaction of trifluoroacetic anhydride adapted for the preparation of cyclic ketones was the acyl addition of carboxylic acids to olefins.[2] Two ω-olefinic acids have



been treated with trifluoroacetic anhydride and one of these, hex-5-enoic acid ($n = 3$), yielded *cyclo*hex-2-enone in good yield. Pent-4-enoic acid ($n = 2$) on the other hand gave



only a trace of *cyclo*pent-2-enone together with a small yield of a linear dimer. The closely related acyl addition of carboxylic acids to acetylenes[2] was also developed for the preparation of cyclic 1 : 3-diketones. Hex-5-ynoic acid ($n = 3$) when treated with



trifluoroacetic anhydride gave a 25% yield of *cyclo*hexane-1 : 3-dione, but pent-4-ynoic acid ($n = 2$) failed to yield *cyclo*pentane-1 : 3-dione, and hept-6-ynoic acid ($n = 4$) failed to yield either *cyclo*heptane-1 : 3-dione or 1-hydroxymethylene*cyclo*hexanone.

Experimental.—Successful cyclisations. (*a*) γ-Phenylbutyric acid[3] (0·18 g.) was dissolved in trifluoroacetic anhydride (0·3 c.c.). The reactants were warmed at 60—70° for 3 hr. and the product was isolated by pouring the mixture into aqueous sodium hydrogen carbonate and extracting it with chloroform. The extract was dried ($MgSO_4$) and the solvent evaporated to leave crude α-tetralone (0·17 g.). The crude product was treated with a methanolic solution of semicarbazide hydrochloride from which α-tetralone semicarbazone (0·17 g.; m. p. 213—214°) was isolated.

In another experiment γ-phenylbutyric acid (0·39 g.) was warmed with trifluoroacetic anhydride (0·6 c.c.) for 1 hr. at 40° and the crude α-tetralone (0·21 g.) isolated as before.

(*b*) Hex-5-enoic acid (8·5 g.) was added to ice-cold trifluoroacetic anhydride (15·6 c.c.). The temperature rose spontaneously to 45°, and the reactants were set aside at room temperature for 2 hr., warmed at 30—40° for 0·5 hr., poured into aqueous sodium hydrogen carbonate, and left overnight. The *cyclo*hexenone was isolated by extraction with chloroform, and the product was distilled under reduced pressure. Three fractions were taken: (i) 0·42 g., n_D^{20} 1·4710, b. p. 50°/20 mm., (ii) 3·06 g., n_D^{20} 1·4860, b. p. 67—68°/18 mm., and (iii) 0·20 g., n_D^{20} 1·4730, b. p. 68—80°/20 mm. (undistilled residue 1·33 g.). Fraction (ii) was essentially pure *cyclo*hex-2-enone. Both fractions (i) and (iii) contained some ketone which was estimated by quantitatively preparing the 2 : 4-dinitrophenylhydrazone, the yields of which corresponded to 0·15 g. and 0·10 g. respectively of ketone, making the overall yield 3·31 g. (46%) [2 : 4-dinitrophenylhydrazone, m. p. 163—164° (Found: C, 52·3; H, 4·35; N, 19·7. Calc. for $C_{12}H_{12}O_4N_4$: C, 52·2; H, 4·38; N, 20·3%). Bartlett and Woods[4] report *cyclo*hex-2-enone, b. p. 61—63°/14 mm., n_D^{18} 1·4842 (2 : 4-dinitrophenylhydrazone, m. p. 163°)].

(*c*) Trifluoroacetic anhydride (8·0 c.c.) was added to hex-5-ynoic acid (5·09 g.) at 0°. After 6 hr., during which the solution darkened considerably, the reactants were allowed to warm to room temperature (18°) and were left overnight. Methanol (30 c.c.) was then added and the mixture was refluxed for 1 hr. before methyl trifluoroacetate and the excess of methanol were

[2] Henne and Tedder, *J.*, 1953, 3628.
[3] Overbaugh, Allen, Martin, and Fieser, *Org. Synth.*, 1935, **15**, 64; 1937, **17**, 97.
[4] Bartlett and Woods, *J. Amer. Chem. Soc.*, 1940, **62**, 2933.

distilled off at atmospheric pressure. The residue was distilled *in vacuo*; the distillate (1·72 g.), a yellow oil, which partly solidified, had b. p. 120—140° (bath-temp.)/0·1 mm. The distillate was rubbed with ether to yield a pale yellow solid, m. p. 99—103°, which was recrystallised from ether–light petroleum to yield *cyclo*hexane-1 : 3-dione, m. p. and mixed m. p. 105° (1·01 g.).

Syntheses of ω-unsaturated acids used in the cyclisation experiments. (*a*) Hex-5-enoic acid. Pent-4-en-1-ol [5] was converted into hex-5-enoic acid by way of 4-bromo- and 4-cyano-pentene according to the method of LaForge, Green, and Gersdorff.[6] The acid used for cyclisation had b. p. 102—104°, n_D^{16} 1·4368 (*p*-toluidide, m. p. 54—55°).

(*b*) Pent-4-ynoic acid was prepared by the oxidation of pent-4-yn-1-ol [7] according to Eglington and Whiting's method.[8] Acid used for the attempted cyclisation had m. p. 55—56°.

(*c*) Hex-5-ynoic acid. 1-Bromo-3-chloropropane (158 g.) was treated with sodium acetylide in liquid ammonia, to yield 5-chloropent-1-yne [9] (56 g.), b. p. 112°/748 mm., n_D^{17} 1·4451. The chloropentyne (55 g.) was refluxed with a solution of sodium cyanide to yield 5-cyanopent-1-yne (35 g.), $n_D^{18\cdot5}$ 1·4362. The cyanopentyne (30 g.) was hydrolysed by 10% sodium hydroxide solution on a water-bath for 6 hr., to yield hex-5-ynoic acid (27·6 g.), b. p. 122—124°/20 mm., $n_D^{18\cdot5}$ 1·4495. Eglington and Whiting,[8] who prepared the cyanide by a different route, report n_D^{17} 1·4409 for the cyanopentyne and m. p. −8°, b. p. 106°/9 mm., n_D^{17} 1·4500, for the acid.

(*d*) Hept-6-ynoic acid. Tetramethylene dibromide (93 g.) was treated with sodium cyanide in aqueous ethanol, to yield δ-bromovaleronitrile [10] (17 g.), b. p. 105—110°/14 mm., n_D^{18} 1·4669 (19·2 g. of tetramethylene bromide were recovered). The bromovaleronitrile (16 g.) with sodium acetylide in liquid ammonia yielded hex-5-ynyl cyanide (8·0 g.), which was hydrolysed with 10% sodium hydroxide solution to hept-6-ynoic acid (6·0 g.), b. p. 78—80° (bath-temp.)/0·04 mm., n_D^{26} 1·4371 (*p*-toluidide, m. p. 80°). Taylor and Strong [11] who prepared hept-6-ynoic acid by a different route report b. p. 93—94°/1 mm., n_D^{25} 1·4495 (*p*-toluidide, m. p. 84—85°).

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[5] Brooks and Synder, *Org. Synth.*, 1945, **25**, 84.
[6] LaForge, Green, and Gersdorff, *J. Amer. Chem. Soc.*, 1948, **70**, 3709.
[7] Jones, Eglington, and Whiting, *Org. Synth.*, 1953, **33**, 68.
[8] Eglington and Whiting, *J.*, 1953, 3052.
[9] Henne and Greenlee, *J. Amer. Chem. Soc.*, 1945, **67**, 484.
[10] Cloke and Ayers, *ibid.*, 1934, **56**, 2144.
[11] Taylor and Strong, *J. Amer. Chem. Soc.*, 1950, **72**, 4264.

272. *The Reversibility of Aromatic Nitration.*

By P. H. GORE.

EXAMPLES of acid-catalysed migrations of aromatic nitro-groups have recently been recorded.[1] These involve two systems (I; R = H or Ac) and (II) in which the central nitro-group slowly moves to give isomeric dinitro-compounds on treatment with concentrated sulphuric acid at 112°.

The scheme suggested [1] for the rearrangement of the dinitroaniline (I; R = H) involves, as an initial step, a reversal of Bamberger's phenylnitramine rearrangement [2] to give the nitramine (III; R = H). The latter either undergoes the normal intramolecular rearrangement to give two of the products isolated, 2 : 5-dinitroaniline and a part, at least, of the 3 : 4-dinitroaniline, or undergoes acidolysis to *m*-nitroaniline. The nitronium cation thus formed is considered to react further with *m*-nitroaniline to give most of the 3 : 4-dinitroaniline, and possibly a little 2 : 5-isomer as well. This is supported by the isolation of a much reduced yield of 3 : 4-dinitroaniline as well as some 15% of *m*-nitroaniline when the rearrangement is carried out in the presence of anisole as acceptor. This observation clearly establishes the presence of a free nitrating agent (presumably NO_2^+) but provides no evidence for a reversal of the phenylnitramine change. In any case, this suggested first step becomes highly unlikely in the reaction with the dinitrophenol (II) (it would involve formation of an analogous phenyl nitrate). Moreover the acidolysis

[1] Pausacker and Scroggie, *Chem. and Ind.*, 1954, 1290; *J.*, 1955, 1897.
[2] Cf. Hughes and Ingold, *Quart. Rev.*, 1952, **6**, 48.

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of phenylnitramine is considerably slower [3] than its rearrangement, whilst Pausacker and Scroggie's mechanism [1] requires the two processes to be comparable in rate.

An attractive alternative mechanism, by which the formation of each of the products may be simply accounted for, involves an acid-controlled removal of the " migrating " nitro-group directly from the dinitro-aniline (I) or -phenol (II), followed by renitration. Such a mechanism seems to require that aromatic nitration is reversible, although it is generally understood to be irreversible. However, evidence now presented shows that such a reversal of nitration is indeed possible, in the special systems here considered.

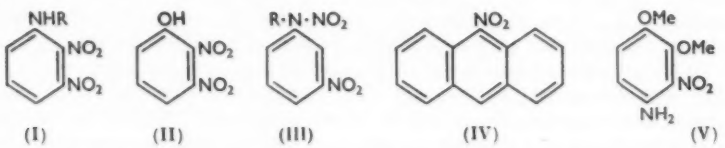
In 9-nitroanthracene (IV) any initial denitration on acid treatment is not followed by nitration in a different aromatic position, as postulated in the above cases, so that the fragments of the acidolysis can be sought. With 12N-sulphuric acid in trichloroacetic acid for 15 min. at 95° it gives a dark solution in which, after dilution with water, an 81% yield of free nitric acid was estimated. Free anthracene could not be isolated, but a 20% yield of anthraquinone * and appreciable amounts of polymer and soluble sulphonic acids were obtained. An experiment conducted in the presence of nitrobenzene failed to show the formation of a possible cross-nitration product. The system may be represented thus :

$$Ar{\cdot}NO_2 \overset{H^+}{\rightleftharpoons} [ArH{\cdot}NO_2]^+ \rightleftharpoons Ar{\cdot}H + \overset{+}{N}O_2$$

$$\downarrow \qquad \overset{H_2O}{\downarrow}$$

$$\text{Products} \qquad HNO_3 + H^+$$

It is seen, therefore, that a nitro-group in an " aromatic " position may be considered hydrolysable (or liable to rearrangement) when its position is activated and is sterically hindered, and the solvent conditions are sufficiently acidic. Activation of the position at which the nitro-group is replaced by hydrogen may occur by electron-releasing substituents (hydroxyl, methoxyl, amino, acetamido), or by the nature of the polycyclic residue. In the present case, the reactive aromatic position is flanked by two bulky *ortho*-substituents, or by two *peri*-hydrogen atoms, so that this central nitro-group may be displaced from the coplanar position with a lowering of its mesomeric deactivation of the ring. Also, if it may be assumed that the transition state of the denitration is a σ-complex,[4] there will be a reduction of steric repulsion by the nitro-group, *i.e.*, there will be little steric hindrance to the formation of the σ-complex. The acid concentration necessary to effect removal of a nitro-group is high in those examples where one of the *ortho*-substituents is a deactivating nitro-group. Thus, rearrangement of the nitrophenol (II) is far from complete after 7 hours with concentrated sulphuric acid at 112°. Where no such deactivation occurs, milder conditions suffice (see Experimental). In one case [5] the nitroaniline (V), where all three substituents are activating, a much less acidic medium (phosphoric acid in glacial acetic acid) can mobilise the nitro-group.



(I) (II) (III) (IV) (V)

We conclude that nitration can be reversed in certain cases, but emphasise that normal aromatic nitrations should continue to be regarded as essentially irreversible, because a nitro-group rarely enters a sterically hindered position of the type discussed here, and

* We do not attempt to explain its formation here.

[3] Cf. Hughes and Jones, *J.*, 1950, 2678.
[4] Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900.
[5] Frisch, Silverman, and Bogert, *J. Amer. Chem. Soc.*, 1943, **65**, 2432.

conditions for the removal of a nitro-group appear to be far more strenuous than those for its introduction.

Experimental.—Action of sulphuric acid on 9-nitroanthracene. 9-Nitroanthracene (5 g.) was dissolved in a mixture of 36N-sulphuric acid (10 ml.) and trichloroacetic acid (30 g.) at 65°, and kept thereat for 10 min., and at 95° for a further 15 min. During this time the odour of " nitrous fumes " was noticeable. The precipitate formed on pouring the mixture on ice was extracted with hot benzene, leaving a black residue (4·5 g.). The dried extract was chromatographed on alumina; the main band (yellow) was eluted, the solvent evaporated, and the residue crystallised from acetic acid, giving anthraquinone (1·0 g., 21%), m. p. and mixed m. p. 283—284°. The aqueous mother liquor gave strongly positive tests for nitric acid (brown-ring, Lunge, " nitron "). Gravimetric precipitation [6] as nitron nitrate (0·287 g. on a 1/25th aliquot part) showed the presence of 1·20 g. (81%) of nitric acid.

I thank Dr. K. H. Pausacker for his comments.

ACTON TECHNICAL COLLEGE, LONDON, W.3. [*Received, May 31st*, 1956.]

[6] Treadwell and Hall, " Analytical Chemistry," John Wiley and Sons, Inc., New York, 1935, Vol. II, 401.

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273. *Anion-exchange Studies of Solutions of Stannic Chloride in Hydrochloric Acid.*

By D. A. EVEREST and J. H. HARRISON.

IT has been recently observed [1] that quadrivalent tin is sorbed by the strong base ion-exchange resin Amberlite I.R.A. 400 from 2M-hydrochloric acid. In view of the utility of ion-exchange methods in the study of complex systems,[2,3] we are studying ion-exchange of solutions of stannic chloride in hydrochloric acid.

The results are given in the Table. The ratios Cl : Sn in the complex tin anions sorbed

Sorption of tin and chloride from solutions of stannic chloride in hydrochloric acid by Amberlite I.R.A. 400-(Cl) (0·25 *g.*).

Acid concn.* (M)	G.-atoms sorbed/ equiv. resin: Cl	G.-atoms sorbed/ equiv. resin: Sn	Cl : Sn in sorbed complex ions: singly charged	Cl : Sn in sorbed complex ions: doubly charged
1·5 ml. of stannic chloride in 50 ml. of solution.				
12	4·00	0·735	5·1 : 1	6·1 : 1
10	4·24	0·760	5·2 : 1	6·2 : 1
10	4·06	0·755	5·0 : 1	6·0 : 1
9	4·15	0·765	5·1 : 1	6·1 : 1
6	4·16	0·755	5·1 : 1	6·1 : 1
5	4·25	0·775	5·1 : 1	6·1 : 1
5	4·15	0·767	5·1 : 1	6·1 : 1
5	4·03	0·765	4·9 : 1	5·9 : 1
4	4·00	0·765	4·9 : 1	5·9 : 1
3	3·60	0·700	4·7 : 1	5·7 : 1
2	3·90	0·720	4·9 : 1	5·9 : 1
1	3·37	0·627	4·8 : 1	5·8 : 1
0·5	3·22	0·627	4·5 : 1	5·5 : 1
0·1	2·84	0·475	4·7 : 1	5·7 : 1
0·02	2·58	0·426	4·5 : 1	5·5 : 1
0·0	1·74	0·292	4·5 : 1	5·5 : 1
0·3 ml. of stannic chloride in 50 ml. of solution.				
1·0	2·65	0·450	4·7 : 1	5·7 : 1
0·5	2·54	0·416	4·7 : 1	5·7 : 1
0·4	2·49	0·423	4·5 : 1	5·5 : 1
0·3	1·62	0·150	5·1 : 1	6·1 : 1
0·25	1·30	0·067	5·4 : 1	6·4 : 1
<0·2	1·00	0·00	—	—

* Acid concentration before addition of stannic chloride.

by the resin, on the assumption that only a simple mixture of chloride ions and n-valent chloro-tin anions were taken up by the resin, were calculated as follows: the fraction of

[1] Hunter and Miller, *Analyst*, 1954, **79**, 483; 1956, **81**, 79.
[2] Everest, *J.*, 1955, 4415.
[3] Holroyd and Salmon, *J.*, 1956, 269.

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the capacity of the resin sample taken up by simple chloride ions was [1 — (n × g.-atoms of tin sorbed)]; the ratio Cl : Sn in the sorbed complex was then given by the expression (g.-atoms of total chloride sorbed — g.-atoms of simple chloride sorbed)/(g.-atoms of tin sorbed). The ratios so calculated indicated that in >1M-hydrochloric acid either $SnCl_5^-$ or $SnCl_6^{2-}$ ions were sorbed by the exchanger. As the amount of tin sorbed was greater than 0·5 g.-atom per equiv. of resin the sorption of $SnCl_5^-$ ions was favoured. As has been shown by Kraus and Moore,[4] in strong hydrochloric acid solutions the anions most strongly held by an anion-exchanger carry the smaller negative charge. This effect is the probable cause of the sorption of $SnCl_5^-$ rather than $SnCl_6^{2-}$ ions by the exchanger.

Hydrolysis was observed with the lower stannic chloride concentrations in <0·25M-hydrochloric acid: hydrous stannic oxide was precipitated and the sorption of tin by the resin fell to zero. No hydrolysis was observed with the higher stannic chloride concentrations, even when hydrochloric acid was not used. Pentachlorostannate or hexachlorostannate ions appeared to be the only tin species sorbed by the resin at all acid concentrations, although the slight decrease in the Cl : Sn ratios in <1M-hydrochloric acid at the higher stannic chloride concentrations may indicate sorption of some partly hydrolysed chlorostannate ions (*i.e.*, some Cl^- ions replaced by OH^-). The fraction of the tin sorbed as these partly hydrolysed species was always small, however, even when hydrochloric acid was not used. In the latter solutions, the chloride ions liberated by the hydrolysis of a fraction of the stannic chloride combine with the rest of the stannic chloride to form penta- or hexa-chlorostannate ions, which were then sorbed by the resin. This would be in agreement with the views of Gueron,[5] who observed that the Raman spectrum of freshly prepared solutions of stannic chloride contained lines observed also in acid solutions of hexachlorostannates.

Experimental.—Stannic chloride (1·5 or 0·3 ml.) was dissolved in 0—12M-hydrochloric acid (50 ml.) and allowed to come to equilibrium with Amberlite I.R.A. 400-Cl resin (0·25 g.) over a period of two weeks. The solution was then separated from the resin phase by filtration through a column (10 cm. long above a sintered glass disc of No. 2 grade porosity), washed with *ca.* 25 ml. of water under suction, the resin-solution contact time during washing being of the order of 10 sec. The resin was then eluted with N-sodium hydroxide (*ca.* 300 ml.), tin in the eluate was estimated iodometrically,[6] and the chloride gravimetrically as silver chloride. As it is not possible entirely to wash out any solution entrained inside the resin beads for fear of hydrolysing the sorbed chloro-tin complexes, an approximate correction was made for entrained chloride by again equilibrating the resin sample with hydrochloric acid of the same normality as was used in the original experiment. The resin was then filtered off, and washed with 20 ml. of water under suction and then slowly with 250 ml. of water. The chloride in the latter washings gave the required correction, small compared with the total amount of chloride sorbed by the resin. The resin sample was finally eluted with *ca.* 250 ml. of 2N-nitric acid, the chloride in the eluate giving the capacity of the resin sample.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, September 18th*, 1956.]

[4] Krauss and Moore, *J. Amer. Chem. Soc.*, 1951, **73**, 10.
[5] Gueron, *Compt. rend.*, 1933, **197**, 247; *Ann. Chim.* (*France*), 1935, **3**, 225.
[6] Everest, *J.*, 1951, 2903.

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274. *Chemistry of Ethyleneimine. Part III.** cyclo*Penteneimine or* 6-*Aza*bicyclo[3 : 1 : 0]*hexane.*

By Paul E. Fanta.

In an earlier paper,[1] the stereochemistry associated with ring-closure and -opening of ethyleneimine was elucidated by a study of *cyclo*hexeneimine. These observations have now been extended to the homologous compound, *cyclo*penteneimine (II).

*cyclo*Penteneimine (II) was prepared by the conventional Wenker procedure from (±)-*trans*-2-amino*cyclo*pentanol hydrochloride (I), and was obtained as a colourless liquid having a strong, unpleasant ammoniacal odour. It was characterized as the *N*-phenylthiocarbamoyl derivative.

Hydrolysis of *cyclo*penteneimine with aqueous perchloric acid gave (±)-*trans*-2-amino*cyclo*pentanol. Since the *cyclo*pentane and aziridine rings can be fused only in the *cis*-configuration, the ring-closure and -opening of *cyclo*penteneimine must occur with inversion at the carbon atom undergoing displacement.

*cyclo*Penteneimine is the first example of a stable, definitely characterized member of the 6-aza*bicyclo*[3 : 1 : 0]hexane system. This skeleton has previously been suggested, without conclusive evidence, for the product of a pyrolysis [2] and also, in the form of an unsaturated iminium derivative, as a possible intermediate in the reaction of 3 : 5-dibromo*cyclo*pentene with dimethylamine.[3]

Experimental.—(±)-*trans*-2-Amino*cyclo*pentanol hydrochloride (I) was prepared as previously described.[4] Hydrogenation of *cyclo*pentanone was accomplished in 99% yield by using freshly prepared Raney nickel without solvent at 60—110° and a hydrogen pressure of 30—120 atm.

(±)-trans-2-*Amino*cyclo*pentyl hydrogen sulphate.* A solution of the hydrochloride (0·289 g.) and sulphuric acid (0·210 g.) in water (2 ml.) was gently heated in an evacuated vessel until the residue solidified. The hard, brown solid was recrystallized from ethanol–water (50%, then 70%) (charcoal) to give fine crystals of (±)-trans-2-*amino*cyclo*pentyl hydrogen sulphate*, m. p. >280° (vigorous decomp.) (Found : C, 33·0; H, 6·2. $C_5H_{11}O_4NS$ requires C, 33·1; H, 6·1%).

cyclo*Penteneimine* (II). A solution of the hydrochloride (I) (13·7 g.) and sulphuric acid (10·0 g.) in water (30 ml.) was evaporated to dryness and gently heated at about 10 mm. for several minutes. Cold aqueous sodium hydroxide (40 g. in 50 ml.) was added and distillation conducted until the residue was nearly solid. The distillate was cooled, saturated with sodium hydroxide, and extracted with ether (15 ml.). The ether solution was dried (Na) and distilled (from Na) to give the imine (5·1 g., 61%), b. p. 115—135°. The middle fraction (2·0 g.) of pure cyclo*penteneimine* had b. p. 122—123°, n_D^{23} 1·4700 (Found : N, 16·6. C_5H_9N requires N, 16·8%). The N-*phenylthiocarbamoyl* derivative, m. p. 167—168° (Found : C, 66·5; H, 6·7; N, 12·8. $C_{12}H_{14}N_2S$ requires C, 66·0; H, 6·5; N, 12·8%), was obtained by treating the imine with phenyl *iso*thiocyanate in light petroleum (b. p. 40—60°)

* Part II, *J. Org. Chem.*, 1956, **21**, 892.

[1] Paris and Fanta, *J. Amer. Chem. Soc.*, 1951, **74**, 3007.
[2] Wolff, *Annalen*, 1913, **399**, 294.
[3] DeWolfe and Young, *Chem. Rev.*, 1956, **56**, 851.
[4] McCasland and Smith, *J. Amer. Chem. Soc.*, 1950, **72**, 2190.

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Hydrolysis of cyclo*pentenei*mine. A solution of *cyclo*penteneimine (0·83 g.) and 60% perchloric acid (1 ml.) in water (3·0 ml.) was refluxed for 30 min. Excess of sodium hydroxide solution and a few drops of benzoyl chloride were added. Warming and shaking followed by cooling gave a white solid, which was recrystallized from methanol–water to give the ON-*dibenzoyl* derivative, m. p. 115·5—116° (Found: N, 4·5. $C_{19}H_{19}O_3N$ requires N, 4·5%). An authentic sample which had an identical m. p. and mixed m. p. was prepared by benzoylation of an aqueous solution of (±)-*trans*-2-amino*cyclo*pentanol hydrochloride as described above for the hydrolysis product.

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275. *Preparation of β-3-Indolylacrylic Acid.*

By J. S. Moffatt.

β-3-Indolylacrylic acid, first prepared by Bauguess and Berg,[1] has been studied as an inhibitor of growth of certain micro-organisms.[2] In our hands, the earlier methods [1,3] gave low and variable yields of a red-brown acid. The indolylacrylic acid was prepared more conveniently and in improved yield (48%) by condensation of 1-acetyl-3-formylindole [4] with malonic acid at 80° and deacetylation of the crude product; the acrylic acid was then obtained as pale-yellow plates. Condensation at 36—40° afforded,[1] in addition to β-3-indolylacrylic acid, mainly (3-indolylmethylene)malonic acid.

Experimental.—Interaction of 1-*acetyl*-3-*formylindole and malonic acid at* 40°. The acetylaldehyde [4] (560 mg.) and malonic acid (936 mg.) were heated in pyridine (4·5 ml.), containing piperidine (3 drops), at 36—40° for 24 hr. The mixture was poured into water and then acidified with 5N-hydrochloric acid. The precipitate was dissolved in 0·5N-sodium hydroxide (18 ml.), and the solution set aside for 1 hr. and then acidified with hydrochloric acid. The resulting yellow precipitate (450 mg.) was extracted with cold ether (30 ml.). The insoluble portion (210 mg.), on repeated crystallisation from methanol, formed minute, yellow needles, m. p. 208—209° (decomp.), of (3-*indolylmethylene*)*malonic acid* (Found: C, 61·7; H, 3·7; N, 6·2%; equiv., 108. $C_{12}H_9O_4N$ requires C, 62·3; H, 3·9; N, 6·1%; equiv., 115). The soluble portion, on fractional crystallisation from ether–light petroleum (b. p. 40—60°), afforded some β-3-indolylacrylic acid (52 mg.).

Interaction at 80°: *preparation of* β-3-*indolylacrylic acid.* The acetylaldehyde (3 g.) and malonic acid (2·52 g.) were heated in pyridine (15 ml.) containing piperidine (0·3 ml.) at 78—80° for 3 hr. The solution was poured into ice-cold water (300 ml.), and the mixture acidified with 5N-hydrochloric acid. After the mixture had been stored in the refrigerator overnight, the yellow precipitate was washed with water and then dissolved in 0·5N-sodium hydroxide (75 ml.). The solution was stored for 1 hr., filtered, and then acidified. The yellow precipitate (1·95 g.) was then dissolved in ether (300 ml.). The solution was filtered, concentrated (to half-volume), and then treated with light petroleum (b. p. 40—60°; 150 ml.). The resulting pale-yellow precipitate on recrystallisation from ethyl acetate afforded 3 crops of the indolylacrylic acid: (i) pale yellow plates (920 mg.), m. p. 192—193° (decomp.) (Found: C, 70·5; H, 5·1; N, 7·6. Calc. for $C_{11}H_9O_2N$: C, 70·6; H, 4·85; N, 7·5%), (ii) pale tan-coloured plates (302 mg.), m. p. 192—193° (decomp.), and (iii) pale tan-coloured plates (234 mg.), m. p. 191—193° (decomp.)

[1] Bauguess and Berg, *J. Biol. Chem.*, 1934, **104**, 675.
[2] Fildes, *Brit. J. Exp. Path.*, 1945, **26**, 416; Marnay, *Bull. Soc. Chim. biol.*, 1951, **33**, 174.
[3] Furst, Harper, Seiwald, Morris, and Nevé, *Arch. Biochem. Biophys.*, 1951, **31**, 190.
[4] Majima and Kotake, *Ber.*, 1925, **58**, 2037.

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[total yield 48%; Bauguess and Berg [1] reported a yield of 34% (from 3-formylindole) of reddish-brown rhombic platelets, m. p. 195—196°].

The author is indebted to Messrs. W. Brown and A. G. Olney for the microanalyses.

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276. *The Preparation of 2-Hydroxyglyoxalines from α-Amino-acids.*

By ALEXANDER LAWSON.

ALTHOUGH 2-hydroxyglyoxaline has been synthesised by the action of cyanate on α-amino-acetaldehyde acetal,[1, 2a] the use of α-amino-aldehydes for the preparation of the 4(5)-substituted homologous 2-hydroxyglyoxalines has not been reported, the 4(5)-methyl,[2b] ethyl,[2a, 3] and phenyl compounds [4] having been obtained from the appropriate amino-methyl ketones. Akabori and Numano [5] prepared a number of 2-mercaptoglyoxalines by the action of thiocyanate on the solutions of amino-aldehydes obtained by the reduction of α-amino-acid esters with sodium amalgam, but did not mention the ring closure with cyanate to give the corresponding oxygen analogues. Owing to the ready accessibility of the α-amino-acids and the improved technique available for the Akabori reduction [5] it seemed of interest to attempt the preparation of some 4(5)-substituted 2-hydroxyglyoxalines by this route.

The method previously adopted for the condensation of amino-aldehydes with thiocyanate [6] cannot be used for the condensation with cyanate, presumably because of the relatively lower stability of cyanic acid. It was found (as with amino-acetaldehyde diethylacetal [2a]) that the temperature had to be kept well below 0° in the initial stages and the pH adjusted to about 7·0. Under these conditions, the yields were satisfactory.

The reaction between cyanate and secondary amino-acetals also takes place readily, as shown by the preparation of 2-hydroxy-1-methylglyoxaline from α-methylaminoacetaldehyde diethyl acetal.

Experimental.—Preparation of 2-hydroxyglyoxalines from amino-acids. The amino-acid (0·05 mole) was heated with ethanol (100 ml.) saturated with dry hydrogen chloride and the solvent removed by distillation under reduced pressure after addition of benzene (50 ml.). The residue of amino-ester hydrochloride was dissolved in ice-cold water (100 ml.), and 2·3% sodium amalgam (200 g.) added slowly with stirring, the pH being maintained between 2 and 3 by the addition of 5N-hydrochloric acid and the temperature held between 0° and −5° by the addition of powdered solid carbon dioxide. The resulting solution was then filtered, cooled to −15° by the addition of carbon dioxide, and brought to pH 4·0 by the addition of sodium hydrogen carbonate, and a cold aqueous solution of potassium cyanate (0·05 mole) added. The pH was then about 7·0. After 30 min. the solution was warmed on the steam-bath for a further 30 min. and finally boiled for several minutes. In the cases of 4(5)-*iso*butyl-, -*n*-butyl-, -*n*-hexyl-, -benzyl-, -*p*-hydroxybenzyl-, and -phenyl-substituted 2-hydroxyglyoxalines the product crystallised from the hot solution. In other cases the product was extracted with ethanol from the solid left after evaporation of the solution under reduced pressure. The m. p., yields, and analyses are shown in Table 1. The monoacetyl derivatives of the hydroxyglyoxalines were prepared on the steam-bath with acetic anhydride–sodium acetate. The analytical

[1] Marckwald, *Ber.*, 1892, **25**, 2354.
[2] Duschinsky and Dolan, *J. Amer. Chem. Soc.*, (*a*) 1946, **68**, 2350; (*b*) 1945, **67**, 2079.
[3] Kolshorn, *Ber.*, 1904, **37**, 2474.
[4] Rupe, *Ber.*, 1895, **28**, 251.
[5] Akabori and Numano, *Ber.*, 1933, **66**, 151, 159.
[6] Bullerwell and Lawson, *J.*, 1951, 2223.

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values and m. p. are in Table 2. A *monobenzoyl derivative* of 2-hydroxy-4(5)-*p*-hydroxybenzylglyoxaline (from tyrosine) had m. p. 242°, prisms from ethanol (Found: C, 69·1; H, 4·9. $C_{17}H_{14}O_3N_2$ requires C, 69·4; H, 4·8%).

2-Hydroxy-1-methylglyoxaline. To a solution of methylaminoacetaldehyde diethyl acetal (7·8 g.) in water (11 ml.) cooled to −15° with solid carbon dioxide, cold 3N-hydrochloric acid (17·5 ml.) and a cold solution of potassium cyanate (6·4 g.) in water (14 ml.) were added. The pH was about 7·0. The mixture, after 30 min. at −15°, was warmed on the steam-bath for 1½ hr.; then after addition of 3N-hydrochloric acid (5 ml.) it was diluted to 100 ml. and heating continued for 2½ hr. The residue left on evaporation under reduced pressure was extracted with hot ethanol, and the *product* (71%) crystallised as prismatic needles, m. p. 219°, after concentration and addition of water (Found: C, 41·0; H, 6·9. $C_4H_6ON_2,H_2O$ requires C, 41·3; H, 6·9%). The *monoacetyl derivative*, needles from ethanol, had m. p. 230° (Found: C, 51·1; H, 5·7. $C_6H_8O_2N$ requires C, 51·4; H, 5·7%).

TABLE 1. *4(5)-Substituted 2-hydroxyglyoxalines.*

Parent Amino-acid	4-Subst.	Form *	Yield † (%)	M. p.	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
Glycine	H	[a]	27	250°	$C_3H_4ON_2$	—	—	—	—
Alanine	Me	[a]	42	202	$C_4H_6ON_2$	48·6	6·1	48·9	6·1
α-Aminobutyric	Et	Plates	37	192	$C_5H_8ON_2$	53·3	7·0	53·5	7·1
Norvaline	Pr^n	Prisms	43	194	$C_6H_{10}ON_2$	56·8	7·9	57·1	7·9
Valine	Pr^i	Needles	44	223	$C_6H_{10}ON_2$	57·3	7·9	57·1	7·9
Norleucine	Bu^n	Prisms	48	191	$C_7H_{12}ON_2$	59·6	8·6	60·0	8·6
Leucine	Bu^i	,,	29	245	$C_7H_{12}ON_2$	59·9	8·6	60·0	8·6
Aspartic	$CH_2{\cdot}CO_2Et$	Plates	56	213	$C_7H_{10}O_3N_2$	49·7	6·1	49·4	5·9
Glutamic	$[CH_2]_2{\cdot}CO_2Et$	Prisms [b]	45	140	$C_8H_{12}O_3N_2$	52·3	6·4	52·1	6·5
Glutamic	$[CH_2]_2{\cdot}CO_2H$	,,	—	246 ‡	$C_6H_8O_3N_2$	45·9	5·3	46·1	5·1
2-Amino-oct-anoic	C_6H_{13}	,,	32	183	$C_9H_{16}ON_2$	63·9	9·3	64·2	9·5
α-Phenylglycine	Ph	Plates [c]	57	325 ‡	$C_9H_8ON_2$	67·3	4·9	67·5	5·0
Phenylalanine	CH_2Ph	Needles	32	238	$C_{10}H_{10}ON_2$	68·9	5·9	69·0	5·8
Tyrosine	$CH_2{\cdot}C_6H_4{\cdot}OH$	Plates	50	254	$C_{10}H_{10}O_2N_2$	62·9	5·5	63·2	5·3

[a] From aq. EtOH. [b] From H_2O. [c] From aq. EtOH.
* From EtOH unless otherwise stated. † Based on the amino-acid used. ‡ With decomp.

TABLE 2. *Monoacetyl derivatives of 4(5)-substituted 2-hydroxyglyoxalines.*

4-Subst.	Form *	M. p.	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
Me	Needles	190° [a]	$C_6H_8O_2N_2$	51·4	5·8	51·4	5·7
Et	,,	170	$C_7H_{10}O_2N_2$	54·5	6·4	54·5	6·5
Pr^n	,,	124	$C_8H_{12}O_2N_2$	56·8	6·8	57·1	7·1
Pr^i	,,	129	$C_8H_{12}O_2N_2$	57·0	6·9	57·1	7·1
Bu^n	,,	120	$C_9H_{14}O_2N_2$	59·5	7·8	59·3	7·7
$CH_2{\cdot}CO_2Et$	,,	95	$C_9H_{12}O_4N_2$	51·0	5·6	51·0	5·7
$[CH_2]_2{\cdot}CO_2Et$	Plates	48	$C_{10}H_{14}O_4N_2$	53·1	6·1	53·1	6·2
$[CH_2]_5{\cdot}CH_3$	Needles	109	$C_{11}H_{18}O_2N_2$	63·2	8·7	62·9	8·6
Ph	Plates	238 [b]	$C_{11}H_{10}O_2N_2$	65·5	4·9	65·4	4·9
CH_2Ph	,,	178	$C_{12}H_{12}O_2N_2$	66·6	5·6	66·7	5·6

[a] Duschinsky and Dolan [2b] gave m. p. 175°. [b] Rupe [4] gave m. p. 157°. * From EtOH.

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